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OCTOBER, 1930

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $6.00

Entered as Second-Class Matter, Jan. 20, 1926, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in the Act of Feb. 28, 1925, authorized Jan. 27, 1926.

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ARCHIVES OF PATHOLOGY

VOLUME 10 OCTOBER, 1930 NUMBER 4

ADDISON'S DISEASE WITH SELECTIVE DESTRUCTION OF THE SUPRARENAL CORTEX

("SUPRARENAL CORTEX ATROPHY")*

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Most cases of Addison's disease are associated with nearly complete destruction of the suprarenal glands, usually by tuberculosis, rarely by secondary neoplasms and amyloidosis. In such cases, no information is offered as to what part of the clinical picture depends on loss of cortical function and what part depends on destruction of the medulla. More instructive are the relatively infrequent cases in which there is found a selective destruction of the cortical elements alone. This condition, often inadequately called "atrophy" of the suprarenal glands, is apparently responsible for about one tenth of the cases of Addison's disease. Thus, among twenty-eight cases observed in the Mayo Clinic and reported by Barker [1] twenty-five presented bilateral tuberculosis and three "advanced bilateral atrophy." Harbitz [2] stated that among twenty-two cases of Addison's disease examined by him, twenty showed tuberculosis and two atrophy of the suprarenal glands. Brenner [3] collected the records of sixty-eight cases of Addison's disease, in thirteen, or 19 per cent, of which "atrophy" of the suprarenal glands was responsible. But many series of cases of Addison's disease have been reported that included no example of this atrophic condition, so that the estimate of 10 per cent is probably not far from the actual proportion.

My own experience is peculiar and difficult to explain. Until a few years ago, I had seen only two cases of Addison's disease unassociated with tuberculosis of the suprarenal glands; one of these was a case with severe amyloid infiltration of the suprarenals; the other was one in which both suprarenals were destroyed by metastatic melanomatous deposits and in which it was difficult to determine whether the clinical picture observed was Addison's disease or merely neoplastic melanosis. In this period, according to my records and my memory, there were approximately twelve cases of Addison's disease. Of the

* Submitted for publication, June 9, 1930.

* From the Department of Pathology, University of Chicago, and the Otho S. A. Sprague Memorial Institute.

1. Barker, N. W.: The Pathologic Anatomy in Twenty-Eight Cases of Addison's Disease, Arch. Path. **8**: 432, 1929.

2. Harbitz: Norsk Mag. f. laegevidensk. **87**:371, 1926.

3. Brenner: Quart. J. Med. **22**:121, 1928.

last nine cases of the disease examined in this laboratory, no less than six have been of the atrophic type, the other three being associated with suprarenal tuberculosis.

The literature of the subject was so recently and so well reviewed by Brenner that it is unnecessary to do more than discuss his presentation, in which are analyzed forty-two of the more recently reported cases of the type under consideration. He found that they could be divided into four groups. In the first group, including eighteen cases, there was marked destruction of the cortex with a relatively intact medulla. In these the greater part of the cortex was destroyed, and "that which remained consisted of islands of very large cells undergoing destruction," associated with varying degrees of fibrosis and round cell infiltration. A second group of eight cases also exhibited a practically normal medulla with entire absence of the cortex. In the third group, of eight cases, there was much damage to both medulla and cortex with considerable round cell infiltration and varying degrees of fibrosis, sometimes with hypertrophy of the remaining cortical cells. In the fourth group, also of eight cases, one or both suprarenal glands were missing or were replaced by a mass of fat or fibrous tissue, with marked damage in whatever surviving suprarenal tissue was found. It is to be noted that in no case did Addison's disease depend on destruction of the medulla with the cortex left approximately intact, and no such case has been convincingly described, as far as I can learn.[4]

The occurrence of a condition in which the cortex of the suprarenal gland is selectively damaged, leaving an abundance of medullary tissue, furnishes a valuable natural experiment demonstrating the vital importance of the cortex and proving beyond doubt that clinically recognizable Addison's disease appears whenever the cortex is destroyed, often despite the preservation of the medulla in a condition in which, as far as morphologic evidence permits one to judge, it should be able to function adequately. These natural experiments on the suprarenal gland offer an unequaled opportunity for securing information on the functions of both cortex and medulla in man, and as such experiments are comparatively rare, each should be considered as carefully as possible. Therefore I present such pertinent information as I have been able to collect concerning the five cases that have come under my observation.

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4. I agree with Brenner that the case reported by Bannwart (Frankfurt. Ztschr. f. Path. **26**:307, 1922) as Addison's disease from bilateral destruction of the suprarenal medulla by metastatic tumors with intact cortex is far from convincingly diagnosed as Addison's disease. Malignant tumors of the abdominal cavity may produce cutaneous pigmentation without any involvement of the suprarenal glands.

REPORT OF CASES

The first case of this series occurred in the practice of Dr. Albert H. Baugher, to whom I am indebted both for the clinical study of the case and for the opportunity to secure an examination of the body at the Illinois Central Hospital, where the death of the patient occurred. Dr. Baugher's clinical report is as follows:

CASE 1.—An unmarried white woman, aged 28, entered the hospital on June 3, 1923, with severe abdominal pain, nausea, vomiting, a temperature of 100 F., a pulse rate of 98, marked bronzed pigmentation of the skin and apparent cardiac insufficiency. The pigmentation was especially pronounced on the face, forearms, backs of the hands, axillae, sides of the hips, knees, outer surfaces of the legs, shoulders and buttocks. There was also slight pigmentation of the mucous membrane of the roof of the mouth. The patient was extremely restless in bed and had alternate fits of laughing and crying. The cardiac insufficiency was not observed at first, but was soon noticed. The blood pressure was 110 systolic until the day of death. Repeated urinalyses showed pale straw-colored urine with a low specific gravity (1.007), positive acetone and diacetic acid, and no albumin or sugar. The abdomen was flat, with apparently no surgical condition present. The condition persisted in gradually increasing severity, and palliative treatment did not amend it to any degree. A tentative diagnosis of acute suprarenal insufficiency secondary to hemorrhage, necrosis or tuberculosis was made. Epinephrine hydrochloride was given intramuscularly, 10 minims (0.6 cc.) every three hours, together with dextrose and solution of sodium bicarbonate twice daily by rectum. An extract of fresh suprarenal gland in salt solution was given intravenously six hours before death, with considerable improvement in the blood pressure. On June 5, forty-eight hours after admission to the hospital, the patient died from progressively increasing cardiac insufficiency.

Past History.—In 1919, the patient had influenza and an attack of appendicitis. She recovered from the latter without operation, and had several attacks later, but they were much less severe. In 1922, she had her tonsils removed but noticed no change in health. On April 20, 1923, she again sought medical aid on account of general lassitude, dysmenorrhea, menorrhagia and anoxemia. Beginning six months prior to this date, she gradually lost vigor, feeling greatly exhausted at the end of the day, but lost no time from work. During the two weeks previous to admission to the hospital she had what she termed an "epidemic cold." (These "colds" were prevalent at this date.) Her tongue was thickly furred; the temperature, blood pressure and pulse rate were normal. The hemoglobin was 80. The color of the skin was that of marked anemia, but pigmentation as an index of disease was not observed at this time, although she stated that it was necessary for her to use cosmetics so that her skin would appear normal. On May 1, the patient entered the hospital complaining of severe abdominal pain at McBurney's point, with nausea and vomiting. She was poorly nourished; the temperature was 100 F., the pulse rate 110, and the respiration rate 24. Severe symptoms had begun at 3 p. m. on the previous day. Immediate operation revealed an acute gangrenous condition of the appendix, which was distended with foul pus. A plastic exudate was found about the appendix, and its mucosa was hemorrhagic and necrotic. The patient's pulse rate while she was in the hospital recovering from the appendectomy remained for the most part between 90 and 100, but before the time of discharge it became stabilized at about 80. Aside from the pulse rate, nothing unusual was noticed in regard to the recovery of the patient,

and she was discharged on May 16. At this time the blood pressure was 110 systolic and 85 diastolic.

Family History.—The patient's father, mother, one brother and two sisters were healthy, except that one sister had an extremely toxic goiter, with marked mental and nervous disturbances, and was considerably improved by a bilateral superior polar ligation and by a later subtotal resection.

Fig. 1.—Selective necrosis of the suprarenal cortex with preservation of the medulla (case 1). The medulla, seen about a central vein, shows no noticeable change from normal. The cortex is completely disorganized. It is indicated only by the dark outer zone, which exhibits no recognizable cortical structures, their place being taken by dilated blood spaces giving the dark color; × 60.

Necropsy.—The body was examined by Dr. E. R. Long. Unfortunately, the opening of the body was limited to a small abdominal incision, and there were other restrictions that prevented a complete examination. The general nourishment was fair, and there were no external abnormalities beyond the scar of a recent appendectomy and a brownish pigmentation, most marked on the face,

forearms, backs of the hands, axillae, sides of the hips and knees and outer surfaces of the lower extremities, shoulders and buttocks. There was but slight pigmentation of the oral mucosa.

The abdominal viscera were normal, except for the absence of the appendix and the presence of a few small cysts in the ovaries. Only the suprarenal glands showed marked changes. They were greatly and equally reduced in size, each weighing 1.1 Gm. They were dark, and the cortex could not be distinguished, except for a few small nodules of the color of cortical substance, each about 1 mm. in diameter. The right suprarenal gland measured 44 mm. long, 8 mm. wide and from 1 to 2 mm. thick. The left was of about the same size.

Microscopically, the abdominal organs showed no marked changes. Unfortunately, it was not possible to obtain the thyroid gland or the thymus. The intestinal lymphoid follicles showed no marked hyperplasia. The suprarenal glands were both greatly reduced in size because of an extreme loss of cortical substance (fig. 1). The cortex contained only a few groups and columns of cortical cells, and these had an unusually homogeneous cytoplasm without the usual granular or vacuolar appearance. The nuclei were mostly small and deep-staining. Some of the cells were extremely large, as if hypertrophied. Considerable areas of the cortex showed no cortical cells, their place being taken mostly by dilated capillaries. There was a slight diffuse infiltration of the cortex with round cells, but little evidence of fibrosis. The loss of cortical material seemed to be chiefly through selective necrosis of the cortical cells with absorption rather than through any severe inflammatory process. In places, traces of the necrotic cells still remained, but generally they had been replaced by dilated capillaries and round cells. Seldom were polymorphonuclears found. The large number of lymphocytes present in the cortex were not so arranged as to suggest a syphilitic process, and there was no formation of scar tissue. The medulla was approximately as thick as normal and showed little change, except that it exhibited several round cell accumulations. Chromaffin material was scanty. The large blood vessels and the capsule showed no changes. The lesions gave no suggestion of tuberculosis, either old or recent. Sections from both suprarenals showed similar pictures.

Apparently, some agent had led to a specific, selective injury of the cortical epithelium. The process seemed to be recent, not all the necrotic material having been removed nor all the cortex destroyed, and little or no evidence of regenerative proliferation being present. The destruction of the cortical parenchyma cells, with absorption of the necrotic material and its replacement by dilatation of the preexisting capillaries, resembled in all essentials the changes seen early in toxic necrosis of the liver (miscalled "acute yellow atrophy"), and the later stages of the two processes, as seen in the following five cases, are also of the same character.

CASE 2.—A woman of 62, a music teacher, whose father was still living at 94, but several members of whose family had died of tuberculosis, had never been strong, but had had no serious illness. About fifteen years before, she had night sweats for a period, leading to a suspicion of tuberculosis. She rested for a year, with apparently complete recovery and no recurrence of this symptom. About two years before death, she began to lose vigor, felt tired and noticed that her skin was slightly yellowish brown. One year before, she had an intestinal disturbance, with diarrhea, diagnosed as "intestinal flu," which kept her in bed two or three weeks. Six months later, she had an acute infection of the upper part of the respiratory tract, which kept her in bed for several weeks. Following this, there was a gradual loss of weight. Again three months later, she caught

cold, and this time vomiting was a conspicuous feature, and for several weeks before death was of daily occurrence.

On examination, three weeks before death, she exhibited marked asthenia, acetone breath and a generalized brownish pigmentation of the skin, especially on the flanks and around the external genitalia, with many dark spots scattered over the face and body. The maximum blood pressure was 90 systolic and 70 diastolic in the left arm, and 75 systolic and 60 diastolic or lower in the right arm, where it sometimes could not be obtained. The basal metabolism was —29.6 per cent. The urine contained albumin, many casts and much acetone. Sugar tolerance was increased. Acute cystitis and the terminal rise in temperature developed. Whole suprarenal gland and an extract of suprarenal cortex were given, without improvement, except a rise in the basal metabolism to —8 and —16.

Necropsy.—Necropsy, performed sixteen hours after death, revealed conditions indicated by the anatomic diagnosis as follows: Addison's disease, with extreme atrophy of the suprarenal glands; slight pigmentation of the skin and gums; aortitis, with a slight aneurysmal dilatation of the ascending aorta and atheroma in the descending aorta; bicuspid aortic valves, with slight diffuse endocarditis fibrosa; fatty infiltration of the wall of the right ventricle; anomalous origin of the left carotid from the innominate artery; brown atrophy of the myocardium; slight chronic glomerulonephritis; slight hyperplasia of the lymph follicles of the colon; healed calcified tuberculosis of the right bronchial lymph nodes; bilateral focal adhesive pleuritis; early acute seropurulent pericarditis; small parovarian cyst; anomalous left suprarenal and renal veins; slight hypostatic pulmonary congestion and edema; lymphoid infiltration of the thyroid; atrophic liver and spleen, and acute esophagitis.

The chief observations of interest were the following:

The body was slender, but not emaciated. There was a distinct brownish-purple pigmentation of the gums, but not of the classic Addisonian type. There was a pigmented light brown area in the skin of the upper part of the abdomen in an area about 5 cm. in diameter. On the sides of the arms, medial thighs and cheeks were small areas of brown pigmentation resembling freckles. There were a few scattered patches or freckles over the arms and wrists and a few over the back. The superficial lymph nodes were not enlarged. The thymus had been replaced by adipose tissue, with no visible remains of thymic tissue. The thyroid gland was slightly enlarged and firm and seemed to have little colloid. It was slightly nodular and apparently hyperplastic, weighing 60 Gm.

The left suprarenal gland was very small, weighing about 4 Gm. and measuring 50 mm. in length, 15 mm. in width and from 2 to 5 mm. in thickness. It was deep brownish red. There were no adhesions or indurations. The right suprarenal was even smaller, weighing 2 Gm. and being reduced to a thin membrane 27 mm. long, 15 mm. wide and less than 1 mm. thick.

Microscopically, the right suprarenal showed many portions in which all the glandular elements had disappeared, only the collapsed fibrous capsule remaining, with the sides in intimate apposition, except for blood spaces and a few small round cells. But in considerable areas the medulla remained, either normal or infiltrated with lymphoid cells and in contact on each side with the capsule (fig. 2). There was some increase in mature fibrous tissue about the central vein, which otherwise was normal. There were also small islands of cortical epithelium, which was far from normal in appearance. The normal parallel arrangement of the cells, with the different zones, was entirely lost. The cortical cells were in strands or rows of irregular size, contour and direction. Often the cells were of remarkably large size, with granular or vacuolated cytoplasm;

again the cells were small, with compact cytoplasm, resembling liver cells. They contained a slight amount of yellowish pigment, not present in the medulla. The nuclei also varied greatly in size and intensity of staining, some being very large. Between these cortical islets were varying numbers of lymphoid and connective tissue cells and a delicate fibrous stroma.

The left suprarenal differed from the right in having no loss of medulla and more of the atypical cortical epithelium remaining (fig. 3). In its bizarre structure, this epithelium recalled the appearance of regenerating liver tissue after acute toxic necrosis, and undoubtedly represents a process of regeneration or

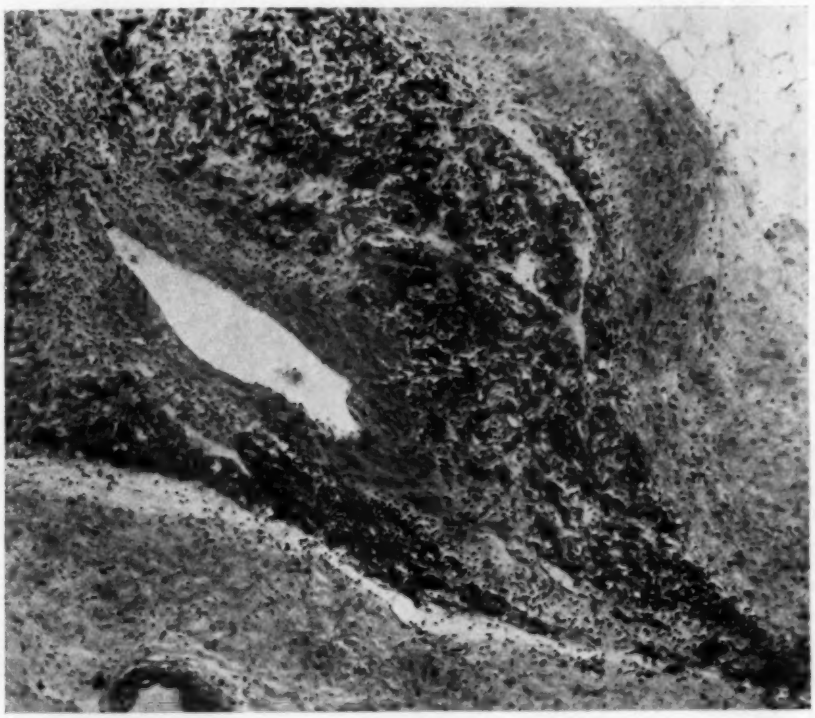

Fig. 2.—In this cross-section of the suprarenal gland intact medullary tissue is seen about a central vein (case 2). There is no cortical tissue, the fibrous capsule on each side lying in direct contact with the medullary substance. Slight lymphoid infiltration of the medullary tissue is to be seen; × 85.

compensatory hypertrophy of the surviving cortical cells.[5] The suprarenals in this case showed more increase in fibrous tissue and less lymphoid infiltration than did those in the other four cases.

5. The extreme deviation from normal that such regenerating cortex cells may exhibit is indicated in the article by Steinbiss (Virchow Arch. f. path. Anat. **262**:286, 1926), which describes what seems to be an extreme case of this type under the title of "Ueber eine eigenartige Degeneration der Nebennieren bei Addisonscher Krankheit."

The thyroid gland presented a most remarkable degree of lymphoid infiltration, some sections being scarcely recognizable as thyroid gland tissue (fig. 4). At least two thirds of the tissue was composed of lymphoid elements, forming well defined lymph follicles with germinal centers which often exhibited marked karyorrhexis. The remaining acini were small and seldom contained colloid. It is significant that in this case, which exhibited a maximum degree of lymphoid infiltration of the thyroid gland, there was nothing elsewhere resembling status

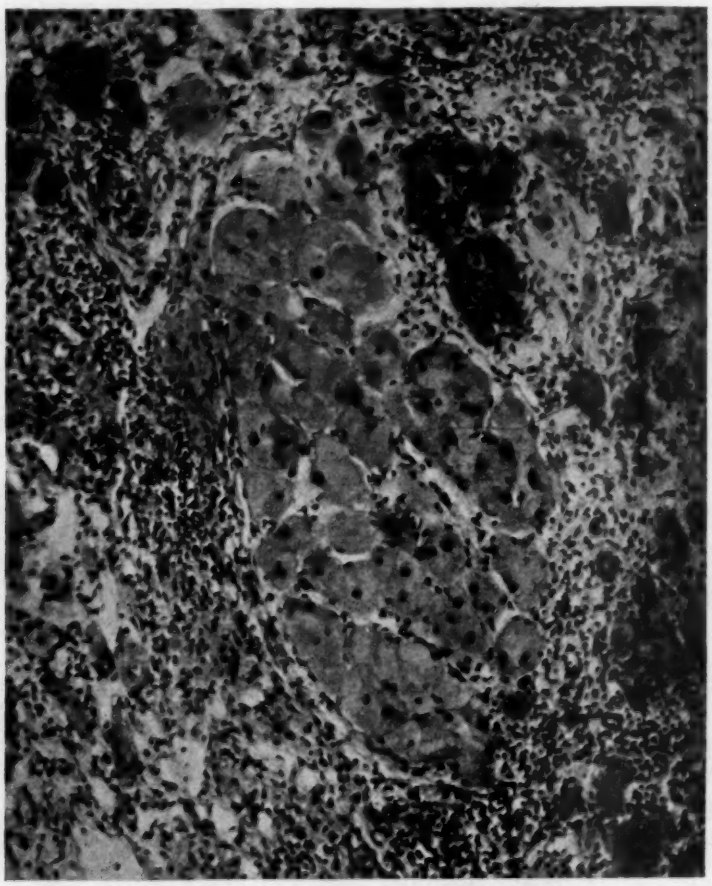

Fig. 3.—Regenerative hyperplasia of persisting cortical epithelium, seen to greater or less degree in all the cases of this series (from case 2). Two types of proliferating cortex cells are seen: one extremely large, often with hyperchromatic nuclei; the other much smaller than normal, seen here adjacent to the group of large cells. There is also diffuse infiltration with small round cells; × 150.

lymphaticus. The lymph nodes were not hyperplastic, and there was almost no lymphoid tissue in the thymic area. Also, the suprarenals showed less lymphoid infiltration than in any of the other cases. Apparently, the lymphoid infiltration of the thyroid and suprarenal glands of this type of Addison's disease cannot be looked on as merely a part of a general status lymphaticus.

CASE 3.—A chauffeur, aged 21, was extremely ill with nausea and vomiting and profoundly prostrated, when first seen by his physician, Dr. Chester Guy, on Jan. 29, 1929. He stated that he had been troubled with attacks of vertigo, nausea and vomiting for two years. This condition had been much worse for the last two months, during which he had lost 20 pounds (9 Kg.) in weight, with increasing severity of the other symptoms.

His previous history included no other illnesses, except influenza. The father was a chronic alcoholic; the mother had had cerebral thrombosis at the age of 40, and had chronic arthritis; one sister was living and well, but another sister was of the asthenic, visceroptotic, hypotensive type; a brother died at the age

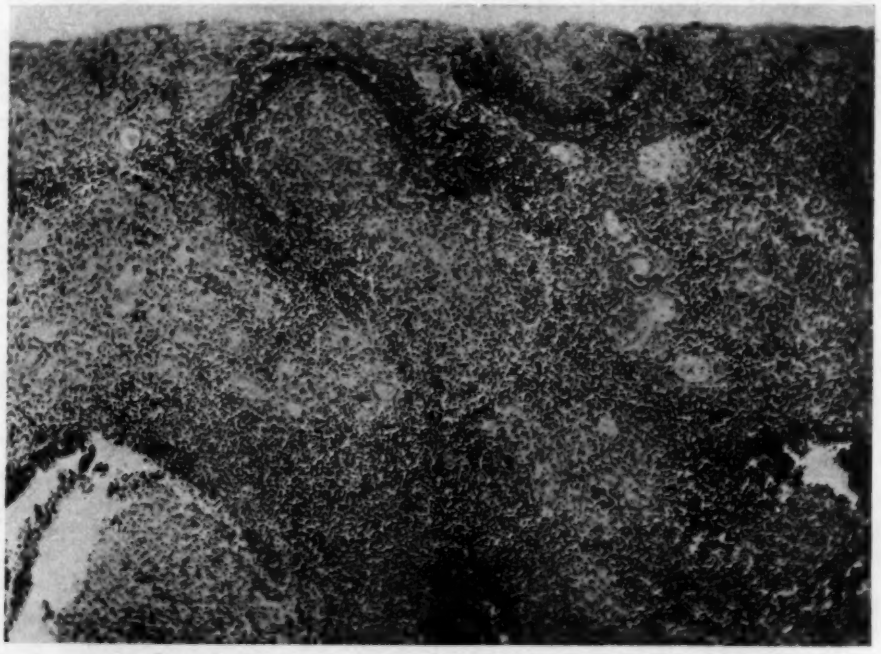

Fig. 4.—Invasion of the thyroid gland by lymphoid tissue as seen in the cases of this series (case 2). In the field covered by the photograph, only occasional atrophic thyroid acini can be detected in a solid mass of lymphoid tissue. The lymphoid tissue presents well developed germinal follicles, so that the picture bears no resemblance to thyroid tissue; × 85.

of 18 from "rheumatism." Nothing could be learned as to habits or past episodes that threw any light on the existing condition.

When examined, the patient complained of being cold, and his temperature was subnormal. The blood pressure could not be recorded because of the circulatory weakness. Physical and laboratory examination revealed little beyond a slightly brownish tinge of the skin without localized pigmentation in either the skin or the oral mucous membrane, a marked dehydration, and albumin and casts in the urine. A clinical diagnosis of Addison's disease was made. Death occurred the next day, January 30, without further developments.

Necropsy.—The postmortem examination by Dr. E. R. Long revealed the abnormalities indicated in the anatomic diagnosis, which was as follows: profound atrophy of the suprarenal glands and moderate diffuse pigmentation of the skin (Addison's disease); moderate hyperplasia of all abdominal lymph nodes and the lymphoid follicles of the ileum; lymphoid infiltration of the thyroid gland; complete atrophy of the thymus; small scattered scars in the lungs, and hypostatic congestion of the lungs.

Fig. 5.—Complete disappearance of both cortex and medulla, the opposite layers of the fibrous capsule of the gland being here separated by a narrow zone of small round cells, with a few endothelial and connective tissue cells (case 3). In other parts of this gland, islands of medullary tissue remain, but no cortex cells; × 150.

The skin was generally slightly brown, most markedly so over the abdomen and the inner aspect of the thighs, but there were no areas of marked pigmentation. There was no evidence of active tuberculosis. The thyroid gland was not enlarged and showed no macroscopically visible alterations.

No definite thymus tissue could be recognized in the adipose tissue of the anterior mediastinum, even microscopically. Apparently replacing the lymphoid elements were islands of vascular adipose tissue of embryonal type with moruloid fat cells.

The lymph nodes in general were not noticeably enlarged, although the malpighian bodies in the spleen and the solitary follicles of the ileum were more prominent than usual, with but slight enlargement of Peyer's patches and none in the lymph follicles of the colon. All other organs seemed normal, except the suprarenal glands.

The left suprarenal was so extremely small that it could hardly be recognized. It lay above the kidney and weighed probably not over 1 Gm. The cortex of this suprarenal could not be distinguished. The right suprarenal was similar to the left, but smaller, weighing from about 0.5 to 1 Gm. The cortex and medulla could not be distinguished. The two organs lay in dark adipose tissue. There were no scars or other evidences of inflammation in the neighborhood.

Microscopically, in the numerous sections examined it was found that the cells of the cortex had completely disappeared. In some places, the blood vessels of the cortex remained and between them were a few cells, apparently endothelial and connective tissue cells and lymphocytes, in many places large accumulations of lymphoid cells having replaced the original cortical epithelium. There was no evidence of tuberculosis or acute inflammatory changes, nor of old or recent hemorrhage. The vessels were not thrombosed or sclerotic. There was little if any increase in fibrous tissue, the original stroma remaining unaltered. The suprarenals were almost exactly alike. In most of the sections, little remained even of medulla, the normal-appearing fibrous capsule having collapsed so that both sides were in apposition for some distance and elsewhere were separated only by blood spaces and small round cells with no trace of glandular elements (fig. 5). Some complete transverse sections of the suprarenal showed only small areas of medullary tissue, generally heavily infiltrated with lymphoid cells. Frequently, the lymphoid accumulations were large and formed masses a millimeter in diameter, without any evidence of a formation of germinal centers. In other sections, large areas of the medulla were well preserved and seemed normal, except for absence of recognizable chromaffin substance. As nearly as can be estimated, less than one fourth of the original medullary tissue remained.

The only cortical cells found were in a small accessory suprarenal, about 2 mm. in diameter, which consisted chiefly of lymphoid cells, an island of medullary tissue and a few small groups of cortical cells separated by stroma elements. These cells did not show the regenerative hypertrophy often seen in cases of this type.

The thyroid gland showed replacement of about 25 per cent of its substance by lymphoid tissue, which existed chiefly in the form of well defined follicles with conspicuous germinal centers that sometimes exhibited karyorrhexis. Some diffuse lymphoid infiltration was also shown, and in some lobules diffuse increase in the interstitial connective tissue. Some lobules appeared nearly normal, but most of them exhibited lymphoid infiltration. In these lobules, the acini were small and poor in, or devoid of, colloid.

The lymph nodes showed a marked increase in lymphoid cells with obscuration of the architecture. The germinal centers were not conspicuous. The nodes showed a markedly nodular surface of mulberry type. The lymph vessels in and about the capsule were often packed with lymphocytes. As stated previously, not a trace of the lymphoid tissue of the thymus body remained; the thymus was completely replaced by fat.

CASE 4.—The course of the disease in case 4 was studied with unusual thoroughness, as the patient, a woman, aged 51 at the time of her death, was under observation for more than four years, and being a person of education and intelligence, gave careful attention to the progress of her condition. She kept an elaborate record of her symptomatology, which will be recorded more fully elsewhere by the clinicians who cared for her, as it is a unique clinical record.

History and Course.—The family history revealed only a tendency to obesity and hypertension in both the paternal and maternal lines and the death of the father from carcinoma of the cecum. The patient had an attack of bronchopneumonia ten years previously; otherwise, although weighing 225 pounds (102 Kg.), she had enjoyed excellent health until four and a half years before her death. Under the direction of an osteopath, she underwent a drastic course of weight reduction with a reducing diet reinforced by a series of electric baths and salt rubs. During six months of treatment, she lost 40 pounds (18.1 Kg.), and at some time in the course of this episode the masseuse noted dark spots on her legs. The loss of weight continued until she weighed 170 pounds (77.1 Kg.). About one and a half years later, she began to notice that she became fatigued easily, had pain between the shoulder blades and was undergoing a deepening of the color of the skin. At this time, twenty-seven months before death, she consulted Dr. Wilber E. Post, who found her blood pressure 102 systolic and 60 diastolic. Whole suprarenal gland tablets were given, apparently with some relief. However, the pain between the shoulder blades continued, and later stiffness in the joints developed. Five months later (Nov. 27, 1927), she entered the Presbyterian Hospital. At this time, it was noticed that the skin was wrinkled as if there had been a loss of weight. Her knees, shins, backs of the hands and finger nails, especially, were brown and black, with black speckled areas of darkened pigmentation. There were black areas on the lips and gums. The areolae of the breasts were hyperpigmented. There was increased dulness on the right side posteriorly from the sixth rib downward on the left. There were no râles. The heart was normal in outline and sound. The abdomen was normal. There were scales on the anterior portion of the tibia and an area of scarring on the right knee. The pelvis showed retroversion and rectocele with blackened vaginal mucous membranes. The chest was normal. There was tenderness in the upper left quadrant, with pain radiating to the neck when pressure was applied. The patient was discharged on Dec. 7, 1927, with the diagnosis of Addison's disease.

She continued to take suprarenal tablets until the latter part of January, 1928, when suddenly they caused her to become nauseated. She vomited bile and all the food that she ate. She then changed to pituitary tablets for two weeks, which did not make her ill; then she changed to Rogoff suprarenal extract for six weeks, which gradually began to cause nausea. She took no suprarenal extract for two weeks and then tried Rogoff's extract once more for from three to four weeks. On April 1, 1928, the blood pressure was 108 systolic and 68 diastolic.

Since Nov. 1, 1928, she had pains low in the back. These started at the hips and ran down to the sides of the knees, chiefly on the right. The pain appeared chiefly at night, rarely before midnight, and occurred every night. She had visual and auditory hallucinations, including those of burglars and ghosts. The patient thought, however, that she was better than one year before, in spite of the increased pigmentation of her skin. At this time, the blood pressure was 115 systolic and 70 diastolic, the basal metabolism was +12, and the other laboratory observations were essentially normal. The pigmentation had become general and

unusually marked for Addison's disease, so that her color was that of a full-blooded negress of medium brown type.

In January, 1929, she entered the Billings Hospital. At this time, the blood pressure was 100 systolic and 68 diastolic. She was weak, becoming exhausted on walking from 50 to 100 yards (from 45.7 to 91.4 M.), and she complained much of pain in the pelvis and left lower extremity. Roentgenograms showed moderate hypertrophic arthritis of the spinal column. The basal metabolism was recorded as + 1 on January 29; on February 11 it was + 3, and on March 1, — 18. She began taking Koehler's extract of suprarenal cortex, but no evident improvement resulted. At times there was much nausea. The blood pressure continued at about 100 systolic and 65 diastolic with slight variation during her stay in the hospital until Feb. 8, 1929.

During the last two years of life, the pigmentation of the skin, which had before then become unusually dark, slowly and progressively faded, although it was still very noticeable at the time of death. There were dark areas in the oral mucosa, especially at the midline of the palate and on the buccal mucosa opposite the gums and teeth.

After leaving the hospital, she remained at home under the care of a nurse until her death. The final illness began three weeks before death, with collapse, sweating and marked relaxation. This was followed by a period of delirium. Neurologic examination showed disturbed reflexes and a bilateral positive Babinski sign, together with other evidences of a lesion of the spinal cord. This cleared up completely in forty-eight hours. Altered reflexes were transiently present at intervals following this. During the last week, the patient was delirious and violent, with intermittent rational phases. There were phases of delusion, and times when the patient would start and scream at the slightest touch. The temperature rose during the last week and reached 105 F. before death.

Necropsy.—The anatomic diagnosis as obtained at necropsy was as follows: Addison's disease; extreme atrophy of both suprarenal glands; diffuse melanotic pigmentation of the skin of the entire body and of the oral and vaginal mucous membranes; slight cardiac atrophy; bilateral diffuse hypostatic pulmonary edema, with diffuse mucopurulent bronchitis; chronic interstitial inflammation of the lungs; terminal septicemia, with ecchymoses in the pleura and pericardium and in the mucosa of the cecum; acute splenic tumor; acute parenchymatous swelling of the liver and kidneys, with slight fatty changes in the liver; acute cerebral edema; acute hyperplasia of the peribronchial lymph nodes; slight edema of the ankles; two diverticula in the duodenum; adhesions about the gallbladder; two fibroid tumors of the uterus; old scar on the outer aspect of the right thigh; marked thickening of the frontal bone, with eburnation; marked adhesions between the dura and the calvarium; absence of axillary hair, and scantiness of pubic hair.

The postmortem observations of particular interest in relation to Addison's disease were as follows:

The skin was a uniform brown color, slightly darker over the lower extremities than over the body proper. The color was about that of a mulatto—somewhat on the order of café-au-lait. The areolae were deeply pigmented. There were no axillary hairs. The pubic hairs were extremely scanty. There was no linea gravidarium, but there were transverse atrophic striae at the umbilicus and at a point 4 cm. above. There was a uniform pigmentation of the mucous membranes of the mouth, comparable in tint to the pigmentation of the skin. The tongue and tissues of the pharynx were edematous. The thyroid gland was of normal size, weighing about 35 Gm.; it was free from nodules, and the cut sur-

face showed no abnormalities beyond a poverty in visible colloid. No traces of thymus tissue could be found.

On first inspection, no trace of either suprarenal gland was seen in the abundant perirenal fat. By following the course of the suprarenal veins, the outlines of the capsules were seen. There was no recognizable cortical tissue, merely a small amount of dark substance separating the fibrous capsule on each side. The right suprarenal was triangular. The suprarenal vein left the organ at the medial angle after a course along the long inferior margin. This margin was adjacent to the kidney and formed the base of the triangle. The apex pointed cranialward. The base was 44 mm., the lateral border 34 mm., the medial 29 mm. and the right 17 mm. The thickness varied between 1 and 2 mm. The weight was 1.2 Gm. The left seemed to be about the same size, although longer and thinner, and its cut surface resembled the right.

The ovaries seemed normal. The vaginal mucosa was diffusely brownish blue. The pineal and pituitary glands were of normal size and appearance. The frontal bone was much thickened (12 mm.) and was composed of dense, hard osseous tissue, but was not abnormally adherent to the dura. The other skull bones were not similarly affected. The brain tissue was edematous, but no other significant cerebral changes were found. The microscopic changes were those characteristic of this type of Addison's disease.

A cross-section through the center of the right suprarenal gland showed that little remained besides the capsule. This was somewhat thicker than normal and through most of the section the two layers of capsule lay almost in apposition, separated only by the central vessels and a few round cells. Occasionally there were small groups of large cells in short cords, not vacuolated like cortex cells and often containing an abundance of brown pigment. Occasionally these cells had extremely large, irregular nuclei. There was one island of tissue about the size of a 16 mm. objective field that seemed to be medullary tissue, which lacked chromaffin. There was no typical cortex tissue in this section. In places there were large groups of lymphoid cells with occasional larger mononuclears, but no evidence of either granulation or scar tissue. No acute inflammation was seen, although there were a few polymorphonuclears infiltrating the capsule. There was considerable granular yellow material in the central space looking as if it might be unabsorbed pigment from the original glandular tissue. It was not contained in phagocytes and did not resemble hemosiderin. There was no evidence of old hemorrhage or thrombosis. The large central blood vessels had a free lumen throughout despite their being collapsed. In other words, nearly all the glandular elements, both medullary and cortical, had vanished from this suprarenal gland, leaving little to take their place beyond the original vessels and stroma and some infiltrated lymphoid cells.

Sections taken through several parts of the left suprarenal gland exhibited much more persisting medullary tissue and more large cells arranged in cords which looked like cortex cells, except that they commonly contained much of the brown pigment that is usually seen in the medulla and they were not vacuolated with lipoids to any marked degree. The large size of these cells and their occasional giant nuclei suggested compensatory hypertrophy. There were also foci of dense infiltration with small round cells. There was a small nodule outside the capsule that apparently was originally an area of accessory cortical tissue. This contained a few scattered parenchyma cells looking somewhat like those found in the rest of the gland, but with less pigment. In various sections of the suprarenal gland were some cells that seemed to be necrotic cortex cells, suggesting

that a process of regeneration and necrosis was still going on to a slight degree. The adipose tissue outside the suprarenal showed slight intercellular edema, and in places islands of primitive adipose tissue could be made out, as the cell structure was not completely obliterated by fat. The adjacent large sympathetic ganglions showed no recognizable changes.

The thyroid gland showed marked infiltration with lymphoid tissue, often forming well defined lymphoid follicles with large active germinal centers in

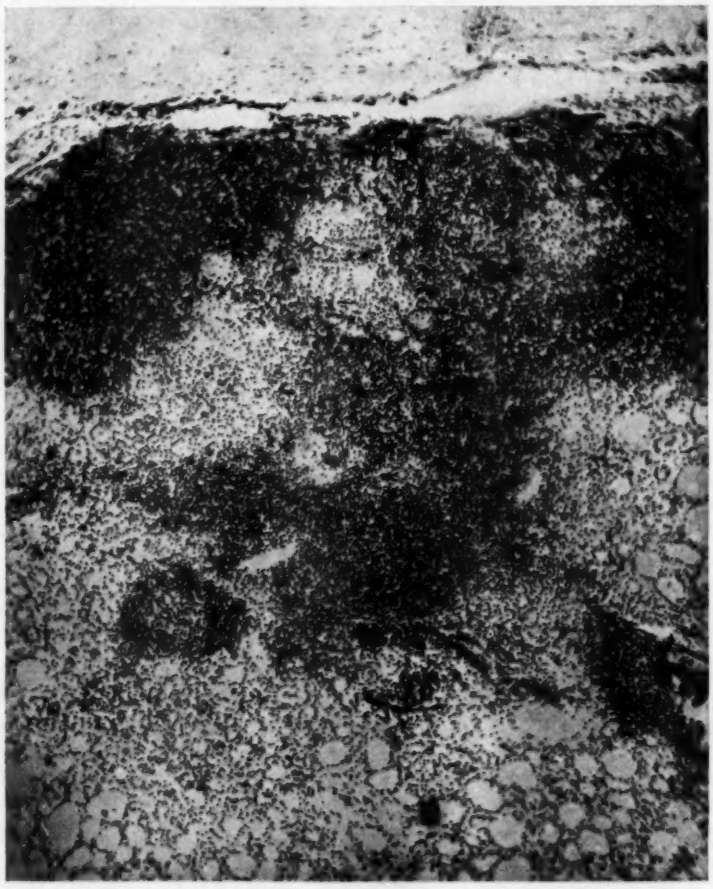

Fig. 6.—The characteristic lymphoid infiltration of the thyroid gland (case 4). In this case, as was the rule, the process is most marked beneath the capsule, the lymphoid tissue invading the thyroid to varying depths, the most central portions showing the least change, although not usually entirely free from lymphoid cells; × 60.

which were occasional mitotic figures (fig. 6). The thyroid tissue was poor in colloid, the majority of the acini containing no colloid and that which remained was greatly vacuolated, as if undergoing absorption. The epithelium was usually large and cuboidal. Some of the acini contained masses of large cells, more

resembling endothelium than epithelium. The arteries were not noticeably sclerotic. There was also much lymphoid infiltration in and about the capsule. One small accessory thyroid gland was found, presenting the same lymphoid infiltration as the thyroid gland itself.

Several small bodies resembling parathyroids in size and location were dissected out. All of these proved to be lymph nodes, except one parathyroid about half replaced by adipose tissue, but otherwise normal. It did not exhibit the lymphoid infiltration seen in the thyroid gland.

The pineal gland seemed somewhat more cellular and of more juvenile appearance than is usual for the age; otherwise it seemed essentially normal. The hypophysis seemed to be entirely normal.

In the spleen there were no marked changes, although the malpighian bodies were larger and more cellular than usual for the age, with slight hyaline changes in the center.

Although the lymphoid tissues were not noticeably enlarged on gross inspection, the small lymph nodes exhibited a distinct increase in the amount of lymphoid cells.

CASE 5.—A woman, aged 40, a patient of Dr. R. K. Packard at the Woodlawn Hospital, was referred to the University Clinics. A history was obtained of progressive weakness for three months, without confinement to bed; loss of 14 pounds (6.4 Kg.) weight in this period, and a darkening of the skin, which was described as "lemon-colored." There was pain in the lower lumbar and sacral regions, and for the last days of life much nausea and vomiting. In the past, the patient's health had been excellent, except that six years before she had been injured in an automobile accident. She was under observation at the Woodlawn Hospital for three weeks before death, during which she showed continued nausea, vomiting, weakness and some increase in the pigmentation.

When admitted to the Billings Hospital, about thirty-six hours before death, she was in an acidotic condition, with reflexes absent, blood pressure 50 systolic and 20 diastolic, blood sugar normal, urine normal, except for a few hyaline casts, and red cell count 3,100,000. She went into coma, with the temperature rising to 105 F. before death.

Necropsy.—The postmortem examination was made twelve hours after death by Dr. P. R. Cannon. The anatomic diagnosis was as follows: bilateral atrophy of the suprarenal glands, with diffuse generalized pigmentation of the skin and buccal surfaces (Addison's disease); generalized atrophy and golden-yellow coloration of the fatty tissues; atrophy and lymphoid infiltration of the thyroid gland; segmentation of the cardiac muscle; chronic fibrous and calcific mitral endocarditis; hypostatic hyperemia and edema of the lungs with compensatory emphysema; bilateral serofibrinous pleuritis; slight ascites; petechial hemorrhages in the pericardial sac and visceral pleurae of both lungs; acute gastritis with confluent hemorrhages in the fundus of the stomach; marked edema of the serosa of the stomach; atrophy particularly of the kidneys, heart, pancreas, liver and generative organs; marked fibrous thickening of the cortex of both ovaries; fibrous tuberculosis of the pleural surfaces of the apexes of both lungs; moderate hyperplasia and anthracosis of the peritracheal, peribronchial and pulmonary lymph nodes, and moderate osteoporosis.

The pigmentation was diffuse, brownish, of moderate degree, without conspicuous dark patches. There were a few patches of brown pigmentation in the buccal surfaces. The lymphoid tissues were not generally increased, only a few lymphoid follicles in the rectum being enlarged slightly. But little recognizable thymus tissue could be found. The suprarenal glands were much decreased in

size, the left measuring 30 by 30 by 2 mm., and the right was slightly larger. Their combined weight was 4 Gm. In sections, no recognizable suprarenal substance could be seen, the appearance being that of a fibrous wall about a cavity.

The thyroid gland was extremely small, weighing but 10.8 Gm., and containing little colloid and no nodules.

Microscopically, the suprarenals showed almost complete loss of the cortical elements, and apparently less than half the medullary tissue remained. In large areas, the capsule, which was somewhat thickened, lay in direct contact with the medulla, there being no remnant of cortex to be found. The medulla showed much infiltration with lymphoid cells, which in some areas completely replaced it, but there were many parts of the medulla that seemed to be normal. In some portions, the cortex had been replaced by connective tissue elements with abundant hyaline intercellular substance so arranged as to suggest that this represented merely a compensatory hyperplasia of the original stroma elements to replace the lost cortex. No vascular changes or evidences of tuberculosis were found. There were occasional small groups of cortex cells, sometimes in nearly the normal arrangement in cords, sometimes entirely disarranged. These cells were not foamy and often were small and atrophic. The total amount of cortex left could not have been more than 1 or 2 per cent of the normal volume. No evidence of regenerative or compensatory proliferation was seen.

The lymph nodes showed a slight but distinct hyperplasia of the lymphoid elements, but less than is usually seen in Addison's disease. Nevertheless, the thyroid gland showed a marked lymphoid infiltration, although less than in the other cases of this series. This seldom reached the extent of forming well developed follicles with germinal centers, but in some of the lymphoid areas were groups of unusually large cells with more abundant and more granular cytoplasm than is usual in endothelial cells, and often with large atypical nuclei. Such cells were not found in the thyroid glands in the other cases. There was little colloid; many lobules contained none, being composed of small collapsed acini and lymphoid cells. Two small accessory thyroids, each about 2 mm. in diameter, showed the same atrophy and lymphoid infiltration as the thyroid gland. The parathyroids showed no lymphoid infiltration and seemed normal, except for marked dilatation of the vessels.

CASE 6.—On May 12, 1930, a woman, aged 47, in extremis, was admitted to the University Clinics. She had been vomiting frequently for twenty-four hours, after having been in bed for a week because of nausea and weakness. In 1922, she had suffered from a period of illness of unknown nature, characterized by extreme nervousness, dizziness, loss of appetite and loss of from 8 to 10 pounds (from 3.6 to 4.5 Kg.) in weight, without localizing pain. This lasted about two years. Thereafter she had never been well and strong. About three months before death she fell and fractured two ribs, after which the weakness began to increase, but no increased pigmentation was noticed by the members of her family. A few weeks following her fall, two teeth were extracted under procaine hydrochloride, after which the weakness seemed to increase. For the lassitude, she consulted a physician, who gave her iron preparations and on April 9 an injection of sodium cacodylate.

When admitted to the hospital, the patient was too ill for complete examination. The temperature was 95 F., the pulse rate was 70, and the blood pressure was 80 systolic and 52 diastolic. A diffuse slight cutaneous melanosis was present, and a little pigment was seen along the midline of the palate. The red count was 5,223,500. The urine contained albumin. The next day, the blood pressure could not be obtained, but on the day of death the systolic pressure was

from 55 to 60. Despite intravenous injections of dextrose, the condition grew progressively worse, and shortly before death the temperature rose to 104.2 F.

Necropsy.—The necropsy was performed one hour after death by Dr. Paul R. Cannon. The anatomic diagnosis was as follows: bilateral atrophy of the suprarenal glands, brownish pigmentation of the skin, hypoplasia of the cardiovascular system and partial persistence of the thymus (clinical Addison's disease); bilateral hypostatic hyperemia and edema of the lungs; bilateral focal fibrous pleuritis; atrophic emphysema; bilateral fibrous tuberculosis of the lungs; moderate hyperplasia of the spleen; chronic pericholycystitis; bilateral fibrous perisalpingitis; chronic fibrous endocervicitis; necrotic and suppurating uterine fibroid; healed fractures of the right tenth and eleventh ribs; moderate atherosclerosis; lymphoid hyperplasia of Peyer's patches in the ileum, and lymphoid infiltration in the thyroid gland.

The chief observations of interest were that the skin was slightly and diffusely brown, except for a single small spot of brown pigment on the left breast. The lymph nodes and lymph follicles of the intestine were not enlarged, although the spleen was slightly enlarged (200 Gm.) with visible follicles. The thyroid gland was small and poor in colloid, and weighed but 13.7 Gm. No active tuberculosis was found anywhere. The bone-marrow of the femur was fatty with occasional islands of hematopoietic tissue. There were healed transverse fractures of the posterior portion of the right tenth and eleventh ribs.

The suprarenals were extremely small, the right weighing 1.5 Gm. and the left 1.4 Gm. There was no induration or adhesion of the tissues about them, and they were soft and flabby. The cut surface showed merely a small amount of dark tissue separating the two layers of the capsule, there being no recognizable cortical substance.

Microscopically, the changes were as follows: Cross-section of the right suprarenal showed that in about one half of the gland nothing remained of either cortex or medulla, the two layers of fibrous capsule lying in apposition. In a considerable portion of the remaining half only medullary tissue remained, with an exaggeration of the chromaffin material in the cells and with much round cell infiltration. There were also nodules of hypertrophied cortex cells, often with large hyperchromatic nuclei. Here the cell columns were irregular and atypical in shape and arrangement. No change occurred in the large vessels and no inflammatory change, unless this was represented by round cells, which were numerous.

The left suprarenal showed more marked cortical proliferation in this case than in any other case in this series, with the usual hypertrophic and atypical cell forms characteristic of regenerating suprarenal cortex. The amount of persisting medullary tissue was not large and was characterized by an abundance of chromaffin material. The amount of round cell infiltration was somewhat less than usual in these cases.

The thyroid gland showed extensive infiltration with lymphoid tissue about the periphery, with formation of occasional lymph follicles showing germinal centers. A striking feature was the packing of lymph vessels with lymphocytes. This lymphoid infiltration was not present throughout the gland, many of the central lobules showing little or none. There was generally a slight increase in interstitial fibrous tissue, and the total amount of colloid was small. Many of the acini were filled with epithelial cells.

The lymph nodes showed a slight increase in lymphoid elements. Peyer's patches were distinctly hyperplastic, with large germinal follicles, but the mucosa elsewhere showed no general lymphoid infiltration.

The thymus showed much more persisting lymphadenoid tissue than is usual for the age. Hassall's corpuscles were numerous, many of which were very cellular. From one half to one third of the thymic body was composed of lymphoid tissue.

The striated muscles showed numerous hyaline muscle fibers, and in general the normal striations were poorly preserved.

COMMENT

These six cases evidently represent examples of clinically typical Addison's disease, diagnosed as such before death, associated only with marked selective loss of suprarenal tissue, especially of the cortex, and independent of tuberculosis or other known agency. In the first case, the process seemed to be somewhat more recent than in the others, and indicated that the essential underlying event in all these cases was a selective necrosis of the cells of the suprarenal cortex, with much less visible injury to the elements of the medulla. All the other changes seen in these suprarenals seemed to be secondary to such a selective necrosis of the cortical epithelium and consisted of inadequate attempts at regeneration of the cortex by proliferation and hypertrophy of the few cortical cells left with sufficient vitality to make these regenerative efforts. There was also a variable amount of loss of medullary tissue, but it was never so marked as that of cortex. It is impossible to tell whether this partial loss of medullary tissue was accomplished in the same way as the cortical damage, or whether it may not have been the result of the extensive lymphoid infiltration that has followed the destruction of the cortex. There was surprisingly little formation of fibrous tissue in these suprarenals, which supports the other evidence that the primary change was not an inflammatory process. Another definite negative observation was that of the absence of any injury or occlusion in the suprarenal blood vessels.

The resemblance to the changes seen in "acute yellow atrophy" of the liver was striking. There was the same apparent selective necrosis of the glandular epithelium, followed by the appearance of large, atypical cells in the process of regeneration and compensatory hypertrophy. There was also a marked infiltration with small round cells of lymphoid character. In the liver, however, connective tissue growth is more marked after extensive necrosis than appeared to be the case in these suprarenals.

The similarity of the changes in "suprarenal atrophy" and "acute yellow atrophy" of the liver suggests a similarity in etiology. It seems to be well established that the latter depends on extensive damage to the liver cells by toxic agents, which may be of most varied character and origin, having only in common the capacity to destroy a large proportion of the liver cells without producing a lethal injury in other tis-

sues. In some cases, the toxic agent is definitely known, in more it is not, and in some cases it seems probable that the severity of the damage depends rather on an unusual susceptibility of the liver cells to the poison than on the amount or quality of the poison. In each case, a selective necrosis of the functional epithelial cells occurs with a minimum amount of injury to other cells, followed by absorption of the dead cells, attempts at regeneration and compensatory hypertrophy by the survivors, and death from loss of the specific functioning cells of the organ. The fact that in this type of Addison's disease both suprarenals are usually involved in the same way and to about the same degree supports the view that the changes depend on some agent entering through the circulation. I believe that the known facts justify as the best designation for this type of suprarenal lesion the term adopted by Kovács,[6] "cytotoxic suprarenal contraction" rather than "suprarenal atrophy," just as the term "diffuse toxic hepatic necrosis" is to be preferred to the misleading name "acute yellow atrophy." Kovác's views are summarized by Omelskyj [7] as follows:

> The conception of the cytotoxic contracted suprarenal concerns a hematotoxic injury selectively affecting the cortex of the suprarenal, while the medullary substance practically escapes. Because the unknown harmful agent is brought by the blood the alterations necessarily are bilateral. Probably the damage is not accomplished at one time but is continued for a long time, against which loss the regenerative capacity of the suprarenal cortex is not adequate, so that the process leads to an extensive disappearance of the cortex with great reduction in size of both suprarenals. The condition may be considered as one in which the cortex cells are slowly damaged, and as the vascular stroma remains unharmed it delivers exudative cells which attend to the removal of the damaged cortex cells, itself remaining and gradually increasing slightly but never being transformed into scar tissue as it is seen to do in those conditions, such as tuberculosis or hemorrhagic infarction, in which the stroma is also destroyed. The less prominent medullary changes are, when present, to be attributed chiefly to secondary unfavorable effects of the adjacent, greatly damaged cortex.

This conception of the condition seems to be entirely in harmony with the facts observed in the cases of this series.

In none of these six cases was there any known episode or condition to account for the destruction of the suprarenal cortex. In case 4, the disease seemed to follow a drastic course in weight reduction, but it is not possible to say that there was more than an accidental relation between the two events. The first case appeared shortly after an operation for acute appendicitis, but suggestive symptoms had been present before; and in case 2, there had been attacks of acute respiratory infections and "intestinal flu." Such events occur too often without any evidence of suprarenal injury to be held responsible, but it is possible

6. Kovács: Beitr. z. path. Anat.. u. z. allg. Path. **79**:213, 1928.
7. Omelskyj: Virchows Arch. f. path. Anat. **271**:377, 1929.

that they may have damaged suprarenals unusually susceptible for some unknown reason. In all but one of these cases there was a definite history of influenza or some similar condition. This fact suggests the possibility of an etiologic relation between influenza and Addison's disease, which would not be impressive, in view of the vast number of cases of influenza without an Addisonian sequel, were it not that it offers a possible explanation of why I have seen all of these cases in the past seven years. Against this assumption is to be placed the fact that other pathologists have not as yet reported any striking recent incidence of this type of suprarenal disease.

The fact that the regenerative processes, although present, are so inadequate suggests the probability that whatever the agent that destroys the cortical cells, it is continuously or intermittently supplied, so that the regenerated cells are also killed off. In case 4, the process was under observation for four years; the cutaneous pigmentation decreased during the last two years; there was much microscopic evidence of regenerative activity in the remaining cortical cells, and yet the course of the patient was slowly downward. Neither the carefully kept history nor the postmortem examination disclosed anything that reasonably accounted for such a long-continued destructive action on the suprarenals.

Age and sex seem to play no rôle, as the cases so far reported are nearly equally divided as to sex, and they have been observed at ages ranging from 10 to 63 years. Fahr and Reiche [8] reported the occurrence of Addison's disease in three brothers in one family, in two of whom the suprarenals showed the atrophic type of lesion (the third was not examined), but there was no information suggesting a common cause, whether hereditary or environmental. Such familial occurrence has not been seen in the other cases reported in the literature.

At times, certain cases of Addison's disease seem to have followed severe mental shock or stress, and a causal relation has been suggested. For example, Marañon [9] reproduced as perhaps the first known case of Addison's disease the description by a priest in the sixteenth century of the sickness of a young priest who died three years after the first symptoms. They developed after a fright; the building in which he was was struck by lightning and burned. The lay description portrays Addison's disease perfectly, but the pigmentation was ascribed to "smoke getting into the system during the fire." Marañon cited modern instances of an emotional origin. One of his patients developed the disease after seeing his child killed by a street car. It certainly does not seem possible that emotional shock could produce tuberculosis of the

8. Fahr and Reiche: Frankfurt. Ztschr. f. Path. **22**:231, 1919.
9. Marañon: Siglo med. **70**:605, 1922.

suprarenal, and hence if there really are cases of Addison's disease resulting from mental causes or nervous stimuli they must come into the group under discussion. But in none of our six cases was there recorded in the clinical history any severe emotional disturbance prior to the development of the disease, except that in case 5 the patient had been in an automobile accident six years before death and in case 6 there had been an accident with fracture of the ribs three months before death and apparently long after symptoms had begun.

From the evidence obtained I can add nothing to the terse summary of Brenner: "The cause is really quite unknown."

It cannot be said that the clinical course of these cases presented any constant differences that make it possible to distinguish such cases during life from Addison's disease due to suprarenal tuberculosis. In some of the cases reported in the literature it was noted that the blood pressure remained at a higher level than is usually the case in Addison's disease, until the terminal collapse. This naturally was attributed to the integrity of the medulla. Most of the cases, however, were not seen until the last stages, in which the blood pressure falls, as it may do in many fatal diseases. In this series, only case 4 was studied for a long period, and here the pressure varied from 100 to 115 systolic. As a matter of fact, the long course of this case, with evidence of some amelioration in the form of a markedly reduced amount of pigmentation, the persistence of the systolic blood pressure above 100 despite long invalidism, and the experience in the preceding three cases led me to hazard the prediction that this type of suprarenal disease would be found underlying the clinical manifestations. Kovács accepted the view that when the suprarenal damage is strictly limited to the cortex, the blood pressure is not greatly depressed, and that the absence of this important feature from the clinical picture should remove the case from the category of typical Addison's disease, and leave cases of the latter to be called cases of "suprarenal cortex insufficiency," which establish the vital necessity of the cortex, while recorded cases of bilateral destruction of the medulla with intact cortex without the Addisonian cachexia demonstrate that destruction of the medulla is not the essential feature of this disease,[10] although it contributes an important clinical feature.

In any case, the fact that in at least some of the cases of destruction of the cortex with intact medulla the blood pressure remains at a good height suggests a reason for questioning the now prevalent acceptance of the doctrine that epinephrine is not a significant factor in maintaining the blood pressure.

Changes in the Thyroid Gland.—A striking feature in all these cases of Addison's disease with suprarenal atrophy was the marked infiltra-

10. The relative rôles of cortex and medulla are well discussed by Omelskyj (footnote 7).

tion of the thyroid gland with lymphoid cells. In all instances, this occurred not only in the form of interstitial collections of lymphoid cells, such as often are seen in the thyroid gland in other conditions, but also the formation of large areas of lymphoid tissue, frequently with well developed germinal follicles. In one case, this lymphoid infiltration was so marked that most of the glandular tissue had been replaced, and the first impression on glancing at the section was of a lymph node with occasional groups of metastatic adenocarcinoma cells.

This infiltration of the thyroid gland with lymphoid tissue has also been described as found in Addison's disease associated with suprarenal tuberculosis,[11] but it seems to be much less marked in this group of cases than in those with selective necrosis of the suprarenal cortex.

Lymphoid Infiltration in Cases of Selective Destruction of Suprarenal Cortex and Cases of Diffuse Tuberculosis of Suprarenal Gland

Selective Destruction of Suprarenal Cortex		Diffuse Tuberculosis of Suprarenal	
Case	Lymphoid Infiltration	Case	Lymphoid Infiltration
1	+++	1	0
2	++++	2	0
3	+++	3	0
4	+++	4	0
5	+	5	0
6	++	6	+
7	+++	7	++
8	++	8	0
		9	0
		10	0
		11	+
		12	0

In order to determine whether this impression is correct I compared the thyroid glands in eight cases dependent on cortical atrophy, five of my own series and three sent me from the Mayo Clinic by Dr. R. G. Mills, two of them having been included in Barker's series and one observed more recently. I graded the degrees of lymphoid infiltration in these eight and compared them with thyroid glands from twelve cases of Addison's disease with tuberculosis of the suprarenals, of which seven specimens were furnished by Dr. Mills and five from my own material.

From the comparison (see accompanying table) it is evident that lymphoid infiltration of the thyroid gland is much more frequent and more marked in Addison's disease due to selective destruction of the cortex than it is in Addison's disease due to suprarenal tuberculosis. In published reports of cases of Addison's disease, it is noticeable that thyroid infiltration is much more often mentioned and discussed in connection with the nontuberculous cases. Brenner noted it in the three

11. Dubois: Berl. klin. Wchnschr. **56**:1178, 1919.

of his cases of cortical atrophy in which the thyroid gland was described, and made the following statement:

> The thyroid gland is also often diseased in Addison's disease, due both to atrophy and to tuberculosis of the suprarenals. In most of the cases described there was some infiltration with lymphocytes and fibrosis. In some cases, as in case 1 described above and Schmidt's cases, the lymphoid infiltration was very dense. In addition, the gland parenchyma often showed changes, either of diminished or of increased activity. In case 1 the changes were as severe as are met with in many cases of myxoedema, yet neither in this case nor in many others described were there any symptoms of deranged thyroid function. In some cases, however, both of atrophy and of tuberculosis the symptoms and pathological changes of Graves' disease as well as of Addison's disease were present, while in other cases there were also symptoms of myxoedema. It seems probable that the changes in the thyroid are due to the same cause as the suprarenal lesion, and not to loss of suprarenal function.

Apparently this lymphoid infiltration of the thyroid gland is not dependent on the general hyperplasia of the lymphatic tissue that so often is found in Addison's disease, for in two cases that I examined in which suprarenal tuberculosis was associated with marked status thymicolymphaticus there was no infiltration of the thyroid gland. Recently I examined the tissues from a case of myasthenia gravis with marked general lymphoid hyperplasia, without any lymphoid cells in the thyroid gland. None of my five cases of thyroid gland infiltration was associated with any marked general lymphoid hyperplasia, and persistent thymus was present only in one. Furthermore, in the third and fourth cases of suprarenal atrophy of this series, no microscopic trace of thymus tissue could be found, despite marked lymphoid infiltration of the thyroid gland. It is also to be remarked that in the cases in which they have been examined, the parathyroids, hypophysis and pineal gland have not shown similar lymphoid infiltration or other abnormality.

The significance of this change in the thyroid gland is not known. It is seen in many other conditions, and Williamson and Pearse,[12] who described it in some detail, look on the thyroid gland showing "lymphadenoid goiter" independent of Addison's disease as "the physiological subnormal gland undergoing hyperplasia." "The lymphocyte reaction is proportional to the failure of the hyperplastic effort and is itself an exaggeration of the normal procedure in the gland." Possibly this condition is related to the low level of metabolism common in these cases of Addison's disease. McCarrison[13] reported that he was able to produce a similar condition in the thyroid of rats by keeping them on a diet in which a deficiency in all vitamins was combined with a deficiency

12. Williamson and Pearse: J. Path. & Bact. **28**:361, 1925.
13. McCarrison: Indian J. M. Research **15**:909, 1928.

of certain inorganic elements, especially manganese, a diet that leads to a state of physiologic subnormality. As yet there is no evidence that diet plays any rôle in producing this condition in man.

SUMMARY

About 90 per cent of all cases of Addison's disease depend on nearly complete destruction of the suprarenal glands, both cortex and medulla, by tuberculosis. Such cases give no indication of the respective rôles played by the cortex and by the medulla. Approximately 10 per cent of the cases exhibit a marked decrease in the size of both suprarenals, which are usually affected about alike, and this "atrophy" is found to depend on an extensive, sometimes an almost complete destruction of the epithelium of the cortex, with less or practically no destruction of the medullary tissues. No cases of undoubted Addison's disease seem to have been observed in which the medulla was found to be destroyed while the cortex was for the most part intact, although cases of such selective medullary destruction without the picture of Addison's disease have been observed. Therefore, the dependence of Addison's disease predominantly on destruction of the cortex of the suprarenal glands seems to be well established by cases in which this condition is present, of which six typical examples are described in this paper.

The cause of the selective destruction of the suprarenal cortex without recognizable corresponding damage to any other tissue in the body is entirely unknown. The bilateral character of the lesion indicates its hematogenous origin. It is not associated with vascular lesions or occlusions. The resemblance both of the tissue damage and the regenerative changes in the surviving cortical epithelium to the processes seen in diffuse toxic necrosis of the liver ("acute yellow atrophy") suggests that the suprarenal condition also is the result of a toxic necrosis by some poison selectively injuring the epithelium of the suprarenal cortex. The histories of the cases so far reported, however, give no satisfactory clue as to the source or nature of the hypothetic poison.

About the only other anatomic change found outside the suprarenal glands is a marked infiltration of the thyroid gland by lymphoid cells, which often form large lymph follicles with germinal centers, replacing much of the glandular tissue. This occurs in the absence of a status thymicolymphaticus, and in two of these cases not even microscopic residues of the thymus could be found. Although lymphoid infiltration of the thyroid gland has been observed in Addison's disease due to tuberculosis of the suprarenal gland, it seems to be less marked and less frequent than in the cases associated with selective destruction of the suprarenal cortex.

CERTAIN SO-CALLED SARCOMAS OF THE THYROID *

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Two years ago, with Dr. Howard S. Clute, I had the opportunity to present a summary of observations on fifty-four malignant tumors of the thyroid gland from the Lahey Clinic. At that time, we proposed a relatively simple grouping of the cases, based primarily on their histology, supplemented by their clinical behavior. This divided the tumors into five groups: (1) the rare epidermoid carcinoma of thyroglossal duct origin, (2) the papillary adenocarcinomas probably of ultimobranchial body origin, (3) the simple adenocarcinomas of "foetal" follicular adenomatous origin, (4) the small round cell tumors of debatable origin and (5) the giant cell tumors frequently presenting many of the generally accepted criteria of sarcomatous mesoblastic origin. On the basis of rather extensive histologic studies, we advanced the belief that all of these tumors were fundamentally epithelial. It was our intention to follow up that preliminary paper with a rather more detailed statement of these individual groups. This report is the first of what we hope to be a series of such papers. Since that time, through the courtesy of their several pathologists, it has been my privilege to compile the cases from the Massachusetts General Hospital, those from the Peter Bent Brigham Hospital, some of the cases from the Boston City Hospital, single cases from several of the smaller suburban hospitals around Boston and finally, through the kindness of Dr. Eugene H. Pool, Dr. Charles L. Gibson and the other staff members of the New York Hospital, the cases that have occurred in the latter institution during the past ten years.

The present paper deals with eighteen cases of malignant disease of the thyroid gland that at one time or another by one or more pathologists have been diagnosed histologically as sarcoma. None of the small round cell tumors most frequently described under the term lymphosarcoma is included in this series, and the term is arbitrarily restricted to that group ordinarily designated as fibrosarcoma.

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* Submitted for publication, May 2, 1930.

* From Cornell University Medical College.

The accompanying table gives the more essential points in respect to the clinical data, as far as it has been possible to secure the facts. Briefly, they may be summarized as follows:

1. The average age in the sixteen cases in which the age was given was 61.2 years, the extremes being 46 and 72 years, respectively.

2. The average postoperative duration in the sixteen cases in which this information could be ascertained was two and four-tenths months. In two of the remaining three cases the patients were dead within a year, and in the final case in this series the patient at the time of writing is dying of recurrence or, perhaps more accurately, of extension of the tumor, four months following operation. The mortality in this group

Giant Cell Tumors

Number	Reference Number	Sex of Patient	Age of Patient	Pre-operative Duration, Months	Post-operative Duration	Total Duration, Months	Result
1	S-21-1158	F	59	1*	2 months	3	Death
2	S-21-1665	M	62	3*	2 days	3	Death
3	S-18-1299	F	71	3*	4 months	7	Death
4	S-24-192	F	57	2	1 month	3	Death
5	DS-24-402	F	60	2*	9 days	2	Death
6	DS-26-068	F	46	4*	1 year	16	Death
7	DS-25-1005	F	53	1*	3 months	4	Death
8	DS-25-1083	F	61	2	4 months	6	Death
9	DS-26-2139	F	69	5*	2 weeks	5.5	Death
10	DS-27-649	F	72	2*	3 months	5	Death
11	DS-27-47	F	54	6	1 day	6	Death
12	DS-25-831	F	71	1*	2 months	3	Death
13	131-11	M	?	?	?	?	Death
14	N. D.	F	69	4	3 months	7	Death
15	M. F.	F	58	3*	1 month	4	Death
16	H-26-403	M	55	2*	2 weeks	2.5	Death
17	39868	F	65	?	?	?	Patient dying at time of writing
18	25318	M	?	2?*	2 months	4	Death
	Average		61.2			4.8	

* Had been present as a nodule for many months or years; recent rapid growth is indicated by figures.

of cases can be considered, therefore, as 100 per cent within a year. Of these deaths, four may be considered as hastened by operation, as the patients died within two weeks after the operation.

3. The incidence in this series is approximately three and a half times as great in women as in men—14 in women and 4 in men. This ratio for the male group is somewhat higher than that of any other type of malignant disease of the thyroid gland that has been studied.

4. All of these cases showed evidence of extension from the original tumor, with invasion of the capsule. On clinical examination, most of them showed involvement of lymph nodes, but unfortunately histologic studies of the nodes were possible in only three of the cases. Three showed definite invasion of the blood vessels, that important histologic criterion of malignancy emphasized by Graham.

These cases therefore constitute a fairly definite clinical group, occurring in persons in the age group above 55 years. The history is

usually one of a rather long continued symptomless goiter, with a small nodular tumor that after months or years suddenly begins to increase in size. The course from then on is rapid, rarely extending for more than six or seven months, and progressing fatally regardless of operative intervention or physical therapy such as that with radium or the x-rays.

After careful histologic study there seems to be little question that in sixteen of these eighteen cases the tumor is epithelial. In two, the epithelial relationship is not so readily apparent, but areas can be found that support the contention which Ewing, Karsner and numerous other investigators have held that these so-called sarcomas of the thyroid gland are epithelial tumors, and that true sarcoma of the thyroid gland has yet to be demonstrated. I have long been of this opinion, and a study of over two hundred malignant tumors of the thyroid gland has tended to confirm this belief.

My purpose in this paper is to illustrate by selected areas from the doubtful cases the reasons for this conclusion. Of all human tissues with which one has to deal microscopically, there is none which normally presents the complexity and multiple variation that the thyroid gland does. And so it is not surprising to find a comparable confusion in the classification of tumors of the gland. Dealing as one does with tissue physiologically so unstable, it is not to be wondered at that its pathologic manifestations are of most bizarre form.

Certain truisms become understandable in relation to histologic study of the thyroid gland—especially that of the need of multiple sections. In the consideration of hardly any other class of tumors, save perhaps of the gliomas, is this so outstanding a necessity. Scarcely any two sections of a tumor of any size from the thyroid gland are comparable; hence the need of studying many different areas becomes apparent before one attempts a diagnosis.

The gross pathologic features of these cases are perhaps the most nearly constant observations. The tumors are usually unilateral, arising from a long standing adenomatous nodule. They grow centrifugally rapidly over a period of a few weeks and attain considerable size, not uncommonly becoming as large as a grapefruit. They frequently extend to involve the opposite lobe, as well. A typical case is shown in figure 3. The rate of growth, as has been stated, is rapid, and the clinical evidence of malignancy is often noted at operation, with the penetration of the thyroid capsule and the involvement of the surrounding structures, even at times the skin, which becomes firmly adherent. The tumor tends to be irregularly ovoid or spherical and frequently superficially nodular, and at times conforms to the general outline of the thyroid lobe.

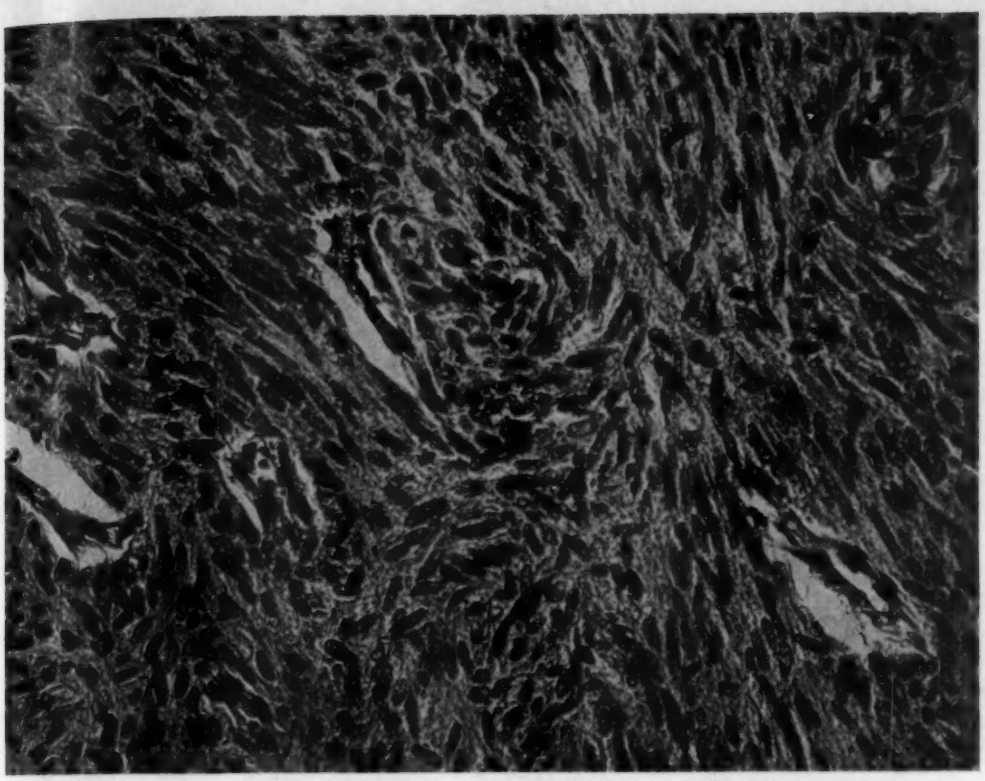

Fig. 1 (case 10).—Spindle cell area from an unmistakable adenoma of the thyroid gland, which in other areas is frankly follicular.

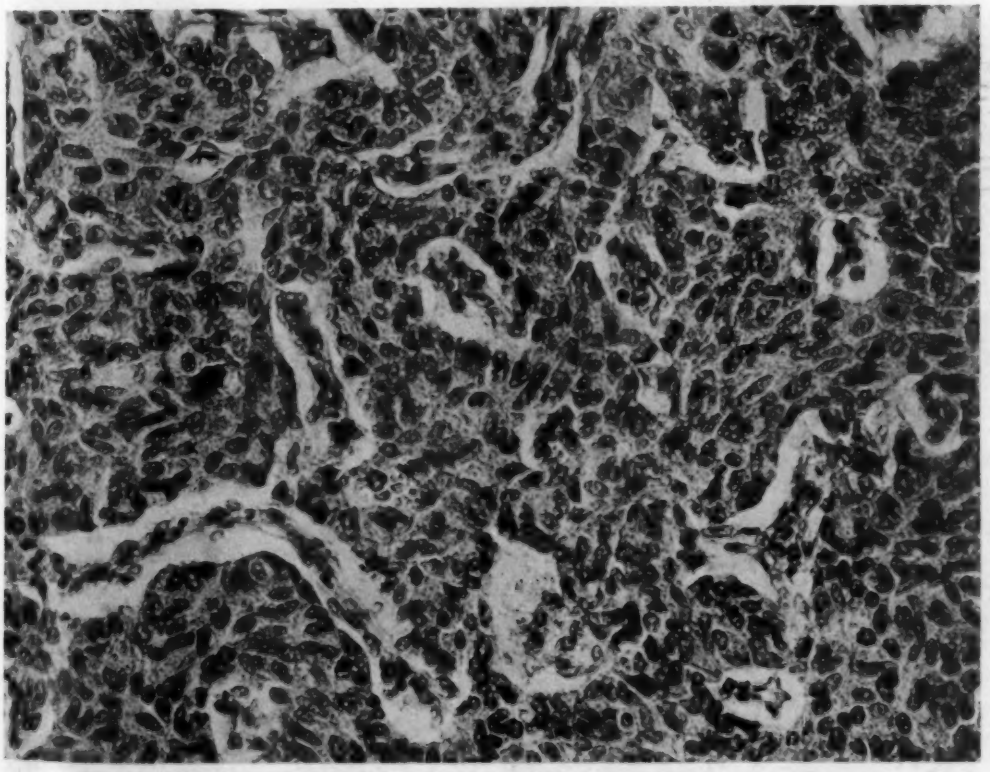

Fig. 2.—Another area from the tumor shown in figure 1. It illustrates the transition of the cells from definite cuboidal epithelium toward the spindle cells noted in figure 1.

Fig. 3 (case 17).—Cross-section of a tumor, actual size, illustrating its adenomatous origin and character.

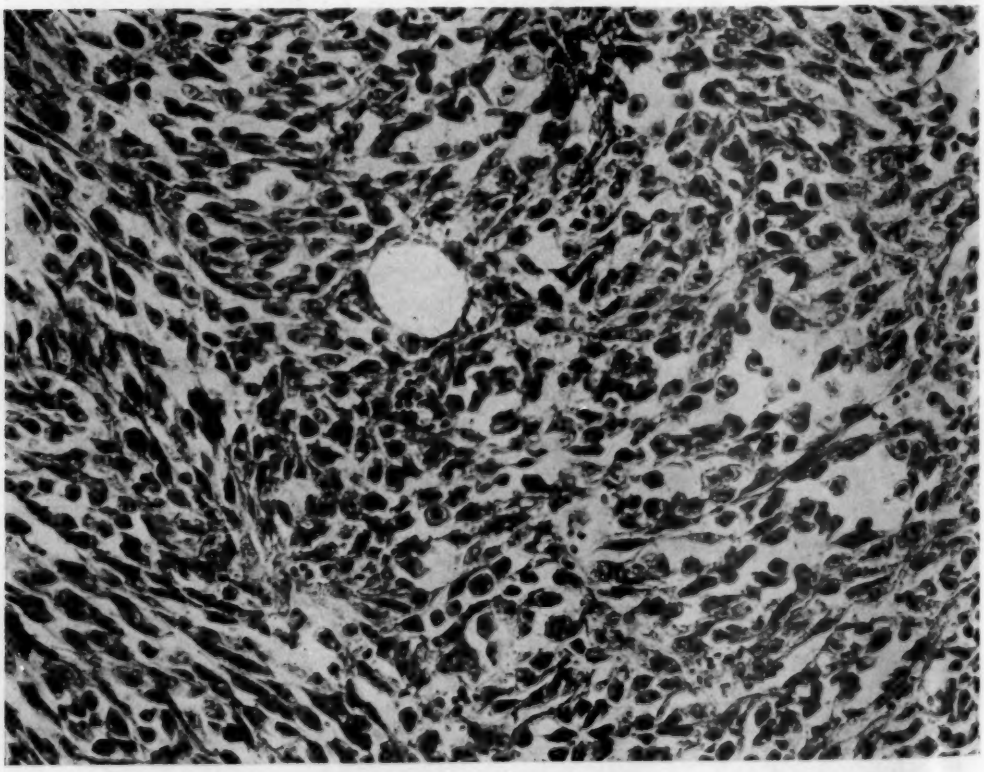

Fig. 4.—A representative field from case 17 (fig. 3). This shows an area of transition where the cells, although still spindle form, are attempting to form pseudo-alveoli.

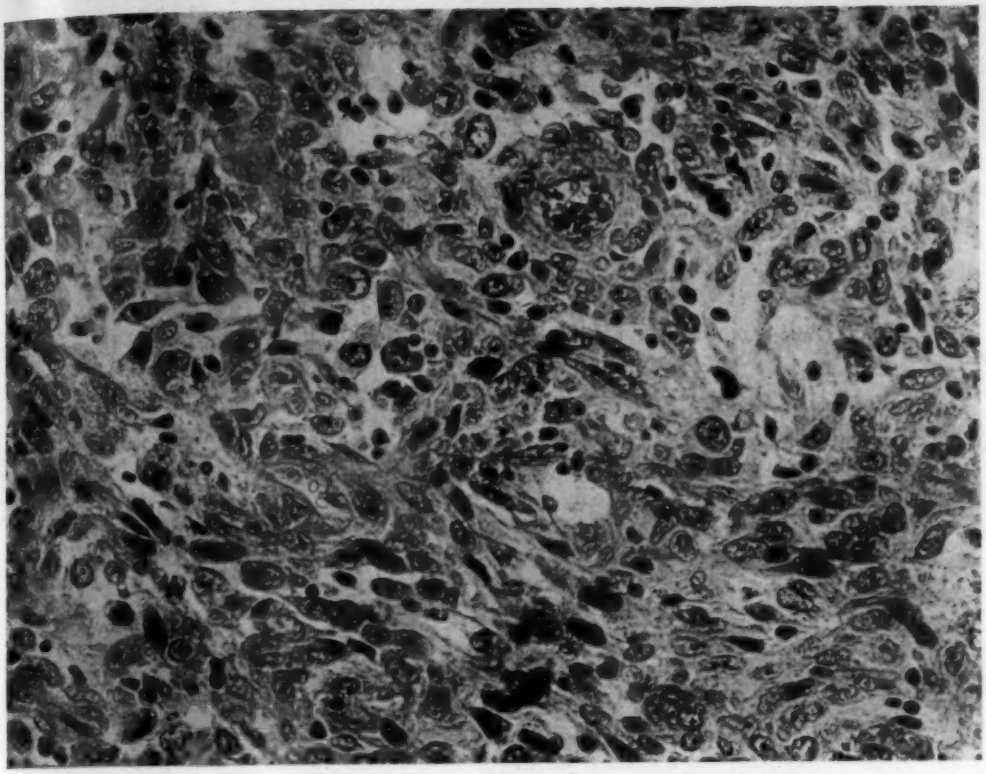

Fig. 5 (case 12).—A case in which it is extremely difficult to demonstrate the epithelial nature of the tumor. Areas of alveolar arrangement can be seen, however, and multiple sections are convincing.

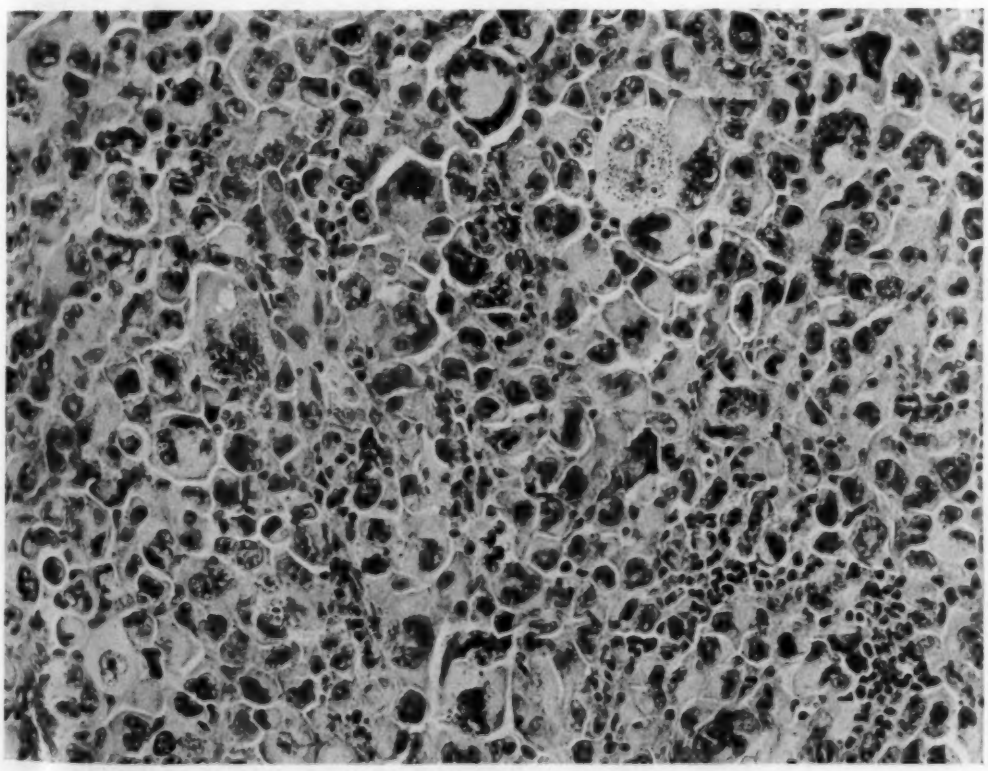

Fig. 6 (case 8).—A carcinoma frankly of the large giant cell type, with alveolar formation. It was diagnosed sarcoma, presumably because of the anaplastic giant cells. The gross specimen shows its adenomatous origin.

On section, these tumors are usually grayish yellow and extremely firm, except where necrosis has occurred, with resultant softening. The architecture is obscure; suggestive strands of trabeculae of connective tissue are visible as a framework for the tumor tissue itself, which is rather more yellow.

Histologically, the picture is essentially one of extremely anaplastic spindlecell overgrowth. The cells assume all sorts of bizarre forms, often with multilobulated nuclei; some appear as multinucleated giant cells. In every one that it has been my privilege to study, I found somewhere evidence of the transition from low cuboidal epithelium to the curious atypical distorted tumor cells. In certain other frankly carcinomatous cases, one can find comparable degenerative changes in the stroma, and it is highly probable that in such cases the stroma may be involved secondarily in a pseudosarcomatous picture. Just as in the case of similar tumors of the breast, of the uterus or of other organs, there is no question as to the primary underlying carcinomatous nature of the tumor, so in the case of these atypical tumors of the thyroid gland there should be no more confusion as to their epithelial nature.

Many obviously adenomatous tumors in which the acinar picture can be easily traced show in portions of the growth a curious spindling of the cells. Such tumors are included among those illustrated in this report for comparison; they emphasize the fallacy of single field photomicrographs or even single microscopic preparations, since individual cases can easily be selected in which the diagnosis is most confusing (figures 1 to 6). As Boyd so clearly brought out in his brief comment on the confusion of nomenclature and differentiation of the "foetal" and "colloid" adenomas, with these sarcomatoid pictures one must take the composite picture into consideration, before arriving at a conclusion. Perhaps the natural history of these tumors is as helpful diagnostically as any other single feature.

They behave more like carcinomas than like sarcomas. They occur in the sixth and seventh decades of life. They metastasize, as a rule, as carcinomas do—by the lymphatic channels and by direct extension, although vascular invasion is by no means uncommon. They can usually be traced to an antecedent adenoma. Both in architectural arrangement and in cytologic detail, they almost regularly have anatomic features in common with thyroid gland epithelium.

Figures 1 to 6 bring out these more important details better than any description can do, and I submit the visual evidence in proof of the contention that an unquestionable mesenchymal type of sarcoma in the thyroid gland has yet to be found.

THE LESIONS IN EXPERIMENTAL AMEBIC DYSENTERY

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(Concluded from page 385)

3. INTESTINAL LESIONS PRODUCED BY INOCULATION IN ANIMALS

DATA FROM THE LITERATURE: LESIONS IN MAN

Following the classic experiment of Lösch [39] (see study 2), interest in an ameba as one of the causes of dysentery was widely stimulated. Kartulis [85] early offered clinical evidence in support of the view that an ameba was concerned in the etiology, while further evidence was presented by him based on a study of the intestinal lesions produced in amebic dysentery, and on the association with these lesions of an ameba corresponding to that described by Lösch. Kartulis [86] reported the first abscess of the liver known to be amebic. He described in moderate detail the pathologic change in amebic ulceration of the intestine and in amebic abscess of the liver, and he expressed the belief that the lesions of the liver arose secondarily to the ulcerative process in the bowel and that the amebas were transplanted to the liver by way of the portal system. He thought, however, that the lesions, both intestinal and hepatic, were primarily produced by bacteria and that the amebas prevented or hindered the healing of the lesions thus produced by their presence in them. He explained the occasional bacteria-free amebic abscess of the liver by assuming that the bacteria present died or were consumed by the amebas after having initiated the destructive changes. Kartulis [87] later departed from this view, believing that amebas, acting alone, might produce intestinal and other lesions. Kartulis [88] was the first to find amebas in an abscess of the brain.

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85. Kartulis, S.: Ueber Riesen-Amöben (?) bei chronischer Darmentzündung der Aegypter, Virchows Arch. f. path. Anat. **99**:145, 1885; Zur Aetiologie der Dysenterie in Aegypten, ibid. **105**:521, 1886.

86. Kartulis, S.: Ueber tropische Leberabscesse und ihr Verhältniss zur Dysenterie, Virchows Arch. f. path. Anat. **118**:97, 1889.

87. Kartulis, S.: Die Amöbendysenterie, in Kolle, W., and Wassermann, A. von: Handbuch der pathogenen Microorganismen, ed. 2, Jena, Gustav Fischer, 1913, vol. 7, p. 651.

88. Kartulis, S.: Gehirnabscesse nach dysenterischen Leberabscessen, Centralbl. f. Bakteriol. **37**:527, 1904.

Osler [89] confirmed the observations of Kartulis concerning amebic abscess of the liver by finding motile amebas in the pus of a hepatic abscess that had been drained surgically. Dock [90] showed that amebiasis is not strictly a tropical disease, and that amebic lesions of the intestine may be present in persons who are free from dysentery and in those who have no history of dysentery.

Councilman and Lafleur [3] published the clinical histories of fifteen patients ill with amebic dysentery, with detailed observations in eight of them, who came to necropsy. Besides abscesses of the liver which occurred in six of the eight, they described, for the first time, amebic abscess of the lung, which occurred in three. In careful observation and detailed description of the lesions, both primary and secondary, this work stands alone and largely serves to establish the general recognition of amebic dysentery as a specific entity.

Further contributions to knowledge of the pathologic changes in amebic dysentery appeared with increasing frequency, so that an attempt to follow them historically becomes a task of great difficulty and of doubtful value. In the following description of the lesions of this disease, an attempt will be made, however, to give credit to those who have made noteworthy contributions to knowledge of the subject.

Intestinal ulcerative lesions due to amebiasis have not been described as occurring elsewhere than in the colon, lower part of the ileum and appendix. The transverse colon is found most frequently involved, with the ascending colon next (Hutchinson,[91] Kuenen [92]). Dopter [4] found the ileocecal valve involved in every case. When the cecum was not specifically mentioned or when it was included with the ascending colon, the upper part of the colon showed the greatest involvement. In the generalized attack on the colon, the more pronounced lesions are still found in the cecum and the ascending colon (Woolley and Musgrave,[93] 159 times in 200 cases; Bartlett,[94] 29 times in 61 cases;

89. Osler, William: Ueber die Dysenterie und dysenterische Leberabscess vorhandene Amoeba, Centralbl. f. Bakteriol. **7**:736, 1890.

90. Dock, George: Observations on the Amoeba Coli in Dysentery and Abscess of the Liver, Centralbl. f. Bakteriol. **10**:227, 1891.

91. Hutchinson, H. S.: Observations on Endamebic Dysentery, J. Lab. & Clin. Med. **13**:613, 1928.

92. Kuenen, W. A.: Die pathologische Anatomie der Amoebiasis vergleichen mit anderen Formen von Dysenteriae, Arch. f. Schiffs- u. Tropen-Hyg. **13**:435, 1909.

93. Woolley, P. G., and Musgrave, W. E.: The Pathology of Intestinal Amoebiasis, J. A. M. A. **45**:1371, 1905.

94. Bartlett, G. B.: Pathology of Dysentery in the Mediterranean Expeditionary Force, 1915, Quart. J. Med. **10**:185, 1917.

Clark [95] in 60 per cent of 186 cases; Rogers,[96] Strong [97]). Next in the order of frequency of localized colonic involvement is the rectum, and then the sigmoid flexure (Hutchinson, Clark), although Kuenen placed the incidence of lesions in the sigmoid flexure before that of lesions in the rectum. Bartlett departed from the views of most writers when he described the finding of advanced lesions in the sigmoid flexure more than twice as often as in the cecum. The splenic and hepatic flexures are less frequently involved (Hutchinson), whereas localized attack of the transverse colon alone is mentioned but once (Councilman and Lafleur). When the condition is uncomplicated, the mucosa around the ulcers and ulcerated areas of the bowel in amebic dysentery is intact and relatively normal. This is held to be typical of intestinal amebiasis (Kaufmann, Rogers,[96] Strong and others).

Amebic ulcers are rarely restricted to one area alone, but may occupy widely separated or contiguous areas in every conceivable combination. Councilman and Lafleur described the simultaneous involvement of the ascending and the transverse colon in one case, of the ascending and descending colon in another case, and of the transverse and descending colon in a third case. In Bartlett's sixty-one cases there were nine in which the lesions were situated generally throughout the colon, with the exception of the rectum.

The appendix is not often ulcerated in amebiasis. Kuenen did not see a case in which it was ulcerated in six years of work at Delhi. Ulceration of the organ does occur, however, for Clark placed it fifth in point of frequency of attack, and Woolley and Musgrave found appendical involvement 14 times in 200 cases. The lower part of the ileum is even less frequently involved than the appendix. Clark did not find any involvement of the appendix in 186 cases, although the ileocecal valve was affected in 5.3 per cent of cases in which there was evidence of generalized colonic attack. Woolley and Musgrave found the ileum ulcerated in 7 of their cases; Bartlett found ileal changes twice, but no amebas were present, whereas Rogers [96] reported mucosal roughening only. Kuenen found the ulcers of the ileum to be smaller than those in the colon, and frequently lying close together.

Harris,[98] from an experience with five cases, was struck by the tendency of amebic ulcers to occupy that portion of the intestine opposite its point of attachment.

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95. Clark, quoted by James, W. M.: Human Amoebiasis Due to Infections with Entamoeba Histolytica, Ann. Trop. Med. **22**:201, 1928.

96. Rogers, Leonard: Dysenteries, Their Differentiation and Treatment, London, Oxford University Press, 1913, pp. 64 and 148.

97. Strong, R.: Amoebiasis, London, Thomas Nelson & Sons, 1920, vol. 2, p. 331.

98. Harris, H. J.: Amoebic Dysentery, Am. J. M. Sc. **115**:384, 1898.

In a more minute examination of the mucosal inequalities which may help to determine the localization of an intestinal ulcer, it has been found by some observers that the summits of the mucosal folds are places of most frequent attack in amebiasis (Rogers,[96] Kruse and Pasquale [99]).

The Preulcerative Period.—Among the intestinal changes of amebiasis there have been described very early lesions that may be looked on as preulcerative. Kruse and Pasquale [99] described intestinal catarrh in two cases, but at the same time found other conditions present that may have explained the observation. Woolley and Musgrave described "red dots," from 0.3 to 2 mm. in diameter, visible on the mucosal surface of the bowel, which were due to hemorrhage into the described tissue of the mucosa. Bartlett described elevated areas about 1 mm. in diameter, with the overlying mucosa not ulcerated. Strong found small, raised hemorrhagic areas involving the submucosa, with later loss of the surface epithelium. Davidson [100] described circumscribed patches of thickening and necrosis of the submucosa which appeared as sharply defined nodules projecting into the lumen of the bowel. He thought the mucosa was involved secondarily. Rogers [101] described dots the size of a pinhead on the inner surface of the intestine, due to congestion and to hemorrhage into the mucosa above earlier exudation into the submucosa. He found amebas in the mucosal tubular glands and thought they reached the submucosa by perforation of the basement membrane. Kaufmann described the initial lesion as infarction-like necrosis of the mucosa, whereas Kartulis [87] found this necrotic plug to be cone-shaped, with its base in the submucosa. He further described hemorrhagic catarrh of the mucosa, characterized by swelling of this tissue, congestion and occasional hemorrhage.

Dopter [4] described mucosal catarrh characterized by minute areas of interglandular thickening, the result of invasion of the connective tissue by cells that destroyed the glandular parallelism. There were found proliferation of glandular epithelium and hypersecretion of mucus, with dilatation of the glandular crypts. There was vascular congestion without hemorrhage, while amebas were present in the blood vessels of the mucosa. In Dopter's [4] "preulcerative lesion" there was enough destruction of tissue to exclude it from consideration here.

Earliest Ulcerative Lesions.—Of the early ulcerative lesions of the bowel recognized as amebic, Harris [98] described superficial erosion of

99. Kruse and Pasquale (footnote 44, second reference).

100. Davidson, Andrew: Amoebic Dysentery, in Albutt, Clifford; and Rolleston, H. D.: A System of Medicine, London, The Macmillan Company, 1909, vol. 2, pt. 2, p. 527.

101. Rogers, Leonard: Further Work on Amoebic Dysentery in India, Brit. M. J. **1**:1315, 1903.

the mucosa involving not more than half of its depth and with no changes in the subjacent submucosa. He did not find amebas in this region, however, and it is thus open to question whether or not this lesion was amebic. Dopter [4] described thickened mucosa with areas of minute superficial erosion. He believed the mucosa was attacked first. Rogers [102] described raised dots about 1 mm. in diameter showing yellow centers, accompanied by great thickening of the subjacent submucosa, above which the mucosal ulcer was narrow. Kuenen described superficial erosion of the mucosa with only congestion of the submucosa. In a study of one case of amebiasis, Christoffersen [103] injected a solution of formaldehyde into the peritoneal cavity immediately after death in the attempt to prevent postmortem changes. Unfortunately, he overlooked the opening of an appendicostomy and applied his fixative solution to the outer surface of the intestine rather than to the mucosa. In this case, he described early ulceration of the outer surface of the mucosa, in which the epithelium and the interstitial tissue were equally involved, and from which the lesion merged smoothly into the surrounding normal mucosa. The submucosa contained only dilated blood vessels. MacCallum [104] stated that the mucosa alone may be involved. James [105] described superficial erosion of the mucosa, recognized only on close inspection and identified as amebic by the presence of *Endameba histolytica* in the lesion. He described the change as solution and destruction of the mucosa, before any appreciable degree of invasion had begun, and said that it might extend for as much as 15 cm. along the surface of the bowel. He thought the amebas attacked the epithelial cells and interstitial tissue with equal facility, thus producing, first of all, a lesion restricted to the most superficial portion of the mucous membrane. He found the underlying vessels congested and thrombosed.

More Advanced Typical Ulcer.—In descriptions of the fully developed amebic intestinal ulcer, there appears to be greater uniformity of opinion than prevails concerning the younger lesions (Delafield and Prudden [106]). Once the mucosa becomes destroyed there is presented an ulcerative lesion that had been looked on from the beginning of the present knowledge of amebiasis as typical of the intestinal process and peculiar to it. This discrete ulcer varies from 1 to 3 cm. in diameter (Rogers [101]), the small ulcers being round and the larger ones oval; the

102. Rogers (footnotes 96 and 100).

103. Christoffersen (footnote 4, second reference).

104. MacCallum, W. G.: A Text-Book of Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1924, p. 770.

105. James, W. M.: Human Amoebiasis Due to Infection with Entamoeba Histolytica, Ann. Trop. Med. **22**:201, 1928.

106. Delafield, Francis, and Prudden, T. M.: A Text-Book of Pathology, ed. 12, New York, William Wood & Company, 1922, pp. 134, 768 and 823.

mucosal edges are red, elevated and undermined, the centers necrotic, gelatinous and yellow, while the submucosa is usually more widely involved than the mucosa above. The base of this ulcer may reach the circular muscle layer, but rarely extends deeper than this.

While the descriptions of the typical amebic intestinal ulcer show remarkable agreement, the same is not true of those of the microscopic appearance. The mucosa beyond the ulcer is found normal (Woolley and Musgrave, Davidson, Viereck [107]) or shows evidences of mucous catarrh (Dopter [4]). The latter is not always widespread, but is frequently limited to a narrow zone immediately surrounding the ulcer (Dopter,[4] Woolley and Musgrave, Viereck) and is characterized by the production of mucous cysts that appear to owe their formation to secretion into glandular crypts that have become occluded at the surface (Viereck). In this zone is found hypertrophy of the mucosa (Woolley and Musgrave), accompanied by an infiltration of small cells between the epithelial columns, increasing in degree as the ulcer is approached (Rogers,[96] Kuenen), dilated blood vessels (Kuenen, Kartulis,[87] Dopter [4]) and occasional hemorrhagic infiltration (Kartulis [87]). The mucosal glands are present and recognizable to the margin of the ulcer (Rogers,[96] Viereck), although they are occasionally distorted and dilated (Davidson). Mucosal destructive changes vary from cloudy swelling of the epithelial cells to necrosis (Kartulis [87]). The epithelial cells become loose and fall into the lumen of the gland. The cells are granular, and the nuclei lose their normal staining reaction, while at the margin of the ulcer the whole becomes a mass of deeply staining detritus (Kruse and Pasquale [99]).

The site of *Endameba histolytica* in the mucosal portion of the typical amebic ulcer of the intestine varies widely, according to the experiences of various observers. Kuenen found amebas below the necrotic area, but never primarily in the glands of the mucosa. Likewise, Harris [98] found them in and between glands at the edge of the ulcer only and never saw an ameba in an intact mucosal crypt. Kartulis [86] however, found them in necrotic tissue and within glands, as did Rogers.[96] Viereck found amebas most frequently in the interglandular connective tissue, and found them rarely in the widened mucosal cysts. Bartlett found *Endameba histolytica* in the mucosa rarely, and Kruse and Pasquale [99] never found them there. Of particular interest is the description by Woolley and Musgrave of the finding of *Endameba histolytica* in the blood and lymph spaces of the interglandular connective tissue. Dopter [4] also found them in the blood vessels of the same region.

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107. Viereck, H.: Studien über die in den Tropen erworbene Dysenterie, Arch. f. Schiffs- u. Tropen-Hyg. **11**:1, 1907.

When the process in the intestine reaches the submucosa, there is developed a necrotic core, which for a time may remain in place (Kartulis[87]). This central necrotic region is composed of granular débris, bacteria and amebas, the whole occupying a space in the submucosa more extensive than that occupied by the mucosal lesions above it (Councilman and Lafleur, Kruse and Pasquale,[99] Harris[98] Dopter[4] and others). Although this resembles a phlegmon of the submucosa (Dopter[4]), it is not purulent (Kruse and Pasquale[99]), and has been described as a coagulation necrosis (Dopter[4]) to which fatty degeneration has contributed a part (Councilman and Lafleur, Kruse and Pasquale[99]). In the older lesions, the central necrotic core is lost, leaving a widely undermined cavity lined with the same necrotic material and surrounded by the tissue of the submucosa, in which are present the changes peculiar to the amebic process, namely, thickening due to edema (Kruse and Pasquale,[99] Woolley and Musgrave, and others), cellular infiltration (Councilman and Lafleur) and dilated blood vessels (Christoffersen and others).

The intestinal thickening in amebiasis may involve all coats (Strong), but it is most marked in the submucosa below and immediately beyond the mucosal lesions (Viereck,[103] Rogers,[102] Strong). Generalized thickening of the bowel has been found more frequently associated with intestinal lesions of bacterial origin than with those of amebiasis (Viereck).

The cellular infiltration of the submucosal portion of the amebic ulcer is largely lymphocytic (Councilman and Lafleur, Harris,[98] Woolley and Musgrave, Rogers,[96] Strong), although polymorphonuclear leukocytes are present in small numbers (Councilman and Lafleur, Kuenen, Harris,[98] Woolley and Musgrave). The presence of the latter in great numbers is looked on as indicating increased bacterial participation (Woolley and Musgrave).

In the necrotic tissue of the wall of the ulcer and within the less changed tissue beyond it, a deposit of fibrin has been observed (Councilman and Lafleur, Kruse and Pasquale,[99] Kuenen), which may reach the surface of the bowel as an attenuated diphtheroid membrane (Dopter[4]). From the evidence presented by special staining methods, however, it has been denied that this material is true fibrin (Viereck).

Beyond the boundaries of the cellular infiltration, the lymph vessels may be found dilated (Davidson), their contents coagulated and unrecognizable (Kruse and Pasquale[99]), and the endothelial lining frequently desquamated (Dopter[4]). More marked changes are found in the adjacent blood vessels, however, which are congested (Woolley and Musgrave, Dopter,[4] Kuenen, Davidson, Bartlett, Christoffersen) and may give evidence of endothelial desquamation (Rogers,[96] Bartlett), endothelial proliferation (Councilman and Lafleur) or thrombosis

(Councilman and Lafleur, Kruse and Pasquale,[99] Viereck, Kuenen, Bartlett). Councilman and Lafleur described obliterative endarteritis of which a feature was thick, edematous walls infiltrated with round cells. Their description of the new formation of capillaries makes it likely that they were dealing with chronic or healing lesions.

Bacteria in small numbers are present in the early intestinal lesions of amebic dysentery (Hutchinson) and are found superficial to the advancing process (Davidson[100]). They are found in greater numbers in the necrotic tissue of the larger lesions (Councilman and Lafleur, Bartlett, Hutchinson) and have been described also as being present in small numbers in the healthy tissue ahead of the advancing amebas (Kruse and Pasquale[99]). Kruse and Pasquale[99] believed that the continued rapid multiplication of the intestinal bacteria after death killed the amebas present and greatly modified the postmortem observations.

In the affected submucosa, *Endameba histolytica* may be found in the necrotic tissue and in the immediate vicinity (Councilman and Lafleur), as well as between the necrotic and near-necrotic portions (Kuenen). In the newly infiltrated regions, they have been found in great masses (Kruse and Pasquale[99]). Although usually found restricted to the immediate region of the ulcer and to the changed tissue of the lesion (Harris,[98] Viereck), they have been described as occurring in the edematous tissue in advance of the acute inflammatory process (Strong) and even, at times, in normal or but slightly altered tissue at a distance (Kruse and Pasquale,[99] Woolley and Musgrave, Christoffersen, Bartlett, MacCallum). Amebas have been found within submucosal lymph spaces (Councilman and Lafleur, Harris,[98] Dopter,[4] Bartlett, Kaufmann, Kofoid,[6] Hutchinson), but even more frequently within the blood vessels of the same tissue (Councilman and Lafleur, Harris,[98] Dopter[4] and others). Harris[98] and Viereck described amebas penetrating the walls of blood vessels, and Viereck found them within blood vessels not thrombosed. Kuenen found them within vessels not thrombosed, as well as within those that were thrombosed. Christoffersen described the amebas as "crowding" the blood vessels in his case, and MacCallum found *Endameba histolytica* within the lumen of the vessel, as well as between the lining endothelium and the wall of the blood vessel.

Late Ulcerative Lesions.—Continued growth of the typical amebic ulcer may lead to fusion with others, resulting in the production of large, irregular ulcers that may reach the size of the palm of the hand (Woolley and Musgrave) or may even encircle the bowel (Bartlett). Early fusion of the submucosal process may produce lesions covered in part by bridges of nearly normal mucosa, deprived of its normal

support from below (MacCallum). Should the base of the ulcer reach the circular layer of intestinal muscles, this tissue is infiltrated with leukocytes (Kartulis [87]) and may be converted into a homogeneous hyaline mass (Councilman and Lafleur). Should the process reach the serosa, there may be present severe edema (James [105]), deposition of lymph, even in the absence of perforation (Rogers [96]), or the development of protective intestinal and omental adhesions (Woolley and Musgrave, Kuenen) or combinations of these. The large lesions contain fewer amebas than the smaller ones (Councilman and Lafleur, Rogers,[96] Hutchinson), increased evidence of bacterial activity and greater infiltration by polymorphonuclear leukocytes (Bartlett, Rogers [101]). Such ulcers, relatively free from necrotic material, may not contain amebas (Bartlett).

Gangrene.—Intestinal gangrene may appear as a complication of the amebic process in the colon (Kartulis,[87] Woolley and Musgrave, Davidson, Kuenen). This change is believed to depend entirely on secondary bacterial invasion of the amebic lesion (Kartulis,[87] Kuenen, Rogers [96]), and the amebas themselves are rarely present in gangrenous regions (Bartlett) and then only in small numbers (Hutchinson). Gangrene may be local or general. The local process occurs most commonly in the cecum, and if the process is general, the more extensive changes are in the cecum (Rogers [96]). This severe lesion leads to an increased incidence of intestinal hemorrhage (Kartulis,[87] Woolley and Musgrave) and of intestinal perforation (Kuenen). In the absence of gangrene, Kuenen found intestinal perforation in amebic dysentery in but one of two hundred cases.

Healing Amebic Lesions of the Intestine.—Healing of the amebic ulcer of the bowel may occur. Clark reported the absence of intestinal lesions in 5.3 per cent of 186 cases that gave evidence of secondary amebiasis at necropsy. The beginning of this reparative change was probably seen in Dopter's [4] "chronic ulcer" in which there were less necrosis, less inflammatory reaction, less pus, less hemorrhage and fewer amebas than in the more active lesions. The floor of the ulcer may be slightly depressed, clean and smooth, and there may be extensive, patchy pigmentation around the partially healed portions (Rogers [96]). Davidson described the formation of clean granulation tissue in the floor of the healing amebic ulcer, and Councilman and Lafleur described the new formation of capillaries in the same region. The latter found the surrounding epithelial cells growing down the walls of the ulcer and across its floor. Small ulcers may heal without a cicatrix (Kuenen), although in the larger ones there are usually scarring and contraction (Woolley and Musgrave, Kuenen, Rogers,[96] Wenyon [5]), with thickening and puckering of the mucosa about the healed portions (Rogers [96]).

Pigmentation of the mucosa around and over healed ulcers has been described (Rogers [96]). Although the ulcerative lesion may disappear, there often remain, as evidence of previous inflammation, mucosal thinning, catarrh with hypersecretion of mucus, loss of normal intestinal folds and atrophy of the intestinal wall, leading to increase in the length of the colon (Woolley and Musgrave). In addition, mucosal atrophy (Dopter [4]) and subsequent formation of intestinal polyps have been described (Dopter,[4] Davidson).

In the attempt to explain the transportation of *Endameba histolytica* from the intestinal lesions to remote organs of the body, participation of the solitary lymph follicles of the colon in the amebic process is of particular interest. In descriptions of intestinal amebiasis, most authors have failed to mention the solitary follicle, thus easily leading to the impression that ulceration beginning in or involving them is not a conspicuous feature of the disease. Kruse and Pasquale [99] did not find follicular change. Davidson believed the solitary follicles remote from the ulcerative processes to be normal, but he described follicular hypertrophy surrounding the portions attacked. The possibility of follicular hypertrophy in amebiasis was mentioned also by Woolley and Musgrave. Specific ulceration of the solitary follicle does occur (Councilman and Lafleur, Dopter,[4] Davidson, Kartulis [87]), although Councilman and Lafleur described secondary involvement of follicles in one case only and believed the follicular attack to be accidental and not to represent a special predisposition on the part of intestinal lymphoid tissue to be invaded by *Endameba histolytica*. Kartulis [87] found ulceration involving the lymph follicles to be rare. When attacked they appeared as small, grayish-white points surrounded by a zone of injection. In the center of each was a small opening on the mucosal surface, below which was a relatively large hole with undermined, elevated and ragged walls. The floor of the follicular ulcer varied from bright red to grayish-yellow, and was occasionally covered with a yellow, fibrinous exudate. Dopter [4] described the wall of the invaded solitary follicle as from rough to ragged, with amebas in great masses present in the wall of the ulcer. Although Kuenen did not find special participation of the follicles of the colon in the amebic process, he believed that there was a selective amebic attack on the aggregated lymph nodules of the lower portion of the ileum, and ascribed one death in typhoid fever to the perforation of a Peyer's patch by amebas.

Regional Lymph Nodes in Amebiasis.—In intestinal amebiasis, invasion of the paracolonic lymph nodes by *Endameba histolytica* appears to be rare. Kofoid [108] mentioned that the lymph nodes adjacent to

108. Kofoid, C. A.: Human Amoebiasis with Special Reference to the Chronic Phase, Texas State J. Med. **21**:347, 1925.

the colon may be invaded, although James [105] saw this in but one case, in which a node adherent to the involved bowel was invaded by direct extension of the amebic ulcer through the wall of the bowel. Howard and Hoover [109] wrote of a "lymphatic barrier" to the wide dissemination of *Endameba histolytica* by way of the lymphatic system, but they did not describe an attack of the mesenteric nodes by amebas. Viereck did not find evidence of involvement of lymph nodes, whereas Dopter [4] described them as red and swollen. Councilman and Lafleur described the mesenteric nodes as softened, swollen and possibly purulent, but denied that they ever contained *Endambea histolytica.* Rogers [96] mentioned slight changes, and Bartlett described slight enlargement, with proliferation and desquamation of the cells of the lymph sinuses, accompanied by increased infiltration with lymphocytes and neutrophilic leukocytes. Among these, the polymorphonuclear cells were relatively few.

Amebic Abscess of the Liver.—Outside of the intestinal tract, the lesion most commonly associated with amebiasis is tropical or amebic abscess of the liver. Descriptions based on postmortem evidence place the incidence of amebic abscess of the liver in cases of amebic dysentery at about 50 per cent (Clark, Knowles), although in a small series of cases the incidence may be as high as six in eight cases (Councilman and Lafleur). Other series have shown, however, that less than half of the patients who die of amebic dysentery have an accompanying hepatic abscess (Strong and Musgrave found fourteen abscesses of the liver in seventy-nine cases; Kuenen, ten abscesses in thirty cases). Among fifty patients who gave but little clinical evidence of intestinal amebiasis and had been free form diarrhea during life, Musgrave [110] found four in whom abscesses of the liver were discovered at necropsy. Depending on clinical rather than on postmortem evidence for his conclusions, Strong believed that in 22 per cent of cases of amebic dysentery abscess of the liver developed and that in from 60 to 90 per cent of cases of abscess of the liver a history of previous dysentery was obtainable. That the modern treatment of amebiasis may reduce the frequency of amebic abscess of the liver as disclosed by necropsy is indicated by the report of Bartlett, who found tropical abscess of the liver but three times in sixty-one cases in which there were amebic intestinal lesions. Nor is this complication peculiar to amebiasis acquired in the tropics. Of forty American patients whose cases were reported by Hutchinson, eighteen had amebic abscess of the liver.

109. Howard, W. T., and Hoover, C. F.: Tropical Abscess of the Liver, with a Consideration of Its Pathology and Clinical History, Am. J. M. Sc. **114**:150 and 263, 1897.

110. Musgrave, W. E.: Intestinal Amoebiasis Without Diarrhea: A Study of Fifty Fatal Cases, Philippine J. Sc. **5**:229, 1910.

Hepatic abscesses due to *Endameba histolytica* are usually single and are found most frequently in the right lobe (Kuenen). Involvement of the left lobe alone seems to be extremely rare, as the abscesses of the left lobe that occurred in 16.4 per cent of Rogers'[96] series were accompanied in all cases by similar processes in the right lobe. He found that in from 55 to 59 per cent of cases there was but a single abscess; in from 23 to 27 per cent more than one large abscess, and in from 17 to 24 per cent one large abscess accompanied by several smaller abscesses. When multiple small abscesses only are found, they may be numerous and then usually involve all lobes of the liver (Councilman and Lafleur). Of the single abscesses in the two cases of Councilman and Lafleur, one lay near the superior surface, near the suspensory ligament, and one lay near the inferior surface in the region of the hepatic flexure.

The amebic abscess of the liver varies in size from a process so small as to be just visible to the unaided eye to one as large as a "child's head" (Kartulis[88]). The small, and probably younger, lesion presents changes in tissue that are looked on as characteristic of the hepatic lesion produced by *Endameba histolytica*. The content of this small, typical lesion is thick, glassy, yellowish mucus (Strong) or, at times, it may be red, due to the presence of blood (Kartulis[86]). When examined microscopically, the material is found to be composed largely of granular detritus, with recognizable fixed tissue elements in small number, fatty (Howard and Hoover) or swollen, generated hepatic cells (Strong), erythrocytes (Kartulis,[86] Councilman and Lafleur, Howard and Hoover, Strong) and a few leukocytes (Strong) or none (Kartulis,[86] Howard and Hoover). If leukocytes are present, they usually are of the mononuclear variety (MacCallum). Fibrin has been described as being present in the content of the abscess (Kartulis[86]), and amebas in great (Councilman and Lafleur) or small numbers (Howard and Hoover) in the content of small lesions. Bacteria frequently are absent (Kuenen, Rogers,[111] Kartulis,[112] Councilman and Lafleur, Kruse and Pasquale,[99] and others), and the material within the abscess cavity is not purulent in the generally accepted sense of this term (Kartulis[113]).

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111. Rogers, Leonard: Tropical or Amoebic Abscess of the Liver and Its Relationship to Amoebic Dysentery, Brit. M. J. **2**:844, 1902; The Prevention and Treatment of an Amebic Abscess of the Liver, Philippine J. Sc. **5**:219, 1910; footnote 96.

112. Kartulis, S.: Zur Aetiologie der Leberabscesse. Lebende Dysenterie-Amöben im Eiter der dysenterischen Leberabscesse, Centralbl. f. Bakteriol. **2**:745, 1887; footnotes 86 and 87.

113. Kartulis (footnote 112, first reference).

In a postmortem examination held within one hour after death, Kartulis [113] found the amebas obtained from a hepatic abscess to be actively motile, and some of them contained two or three ingested erythrocytes.

The wall of the small hepatic lesion is ragged, irregular, soft, grayish white (Howard and Hoover) and without a fibrous capsule (Kartulis,[86] Councilman and Lafleur, Kuenen, Bartlett). The change is that of necrosis of the liver, accompanied by a slight inflammatory reaction (Kuenen). Councilman and Lafleur did not find a definite restricting wall; they found only shrunken and broken hepatic cells, with no encircling inflammatory tissue. From within outward, Kartulis [86] divided the wall of the abscess into three zones; the first, or inner, zone was made up of granular débris in which was imbedded fibrin, cellular and nuclear fragments, amebas and, rarely, bacteria. By gradual transition, zone 1 entered zone 2, where were found large cells with granular cytoplasm and indefinite nuclei, some granulation tissue and "young" bile ducts. Beyond this, in zone 3, he found loosened hepatic cells that had become spindle-shaped as the result of the pressure of the dilated and thickened blood vessels and of the infiltration with leukocytes and plasma cells. In the layer of granulation tissue described by Bartlett as forming a part of the wall of the abscess, he observed infiltration with lymphocytes, plasma cells and a few polymorphonuclear leukocytes. Kartulis [86] found amebas in the abscess cavity and found them in larger numbers in the necrotic tissue of the wall and among the changed hepatic cells and within the capillaries of the outer zone. Bartlett found them in the débris close to the wall, in the layer of granulation tissue and in the blood vessels of it. Strong found them mostly in the wall of the abscess, whereas MacCallum described them as seen at the point of greatest change in tissue. Koch and Gaffky [114] described an abscess of the liver with cocci present in the wall of the cavity and amebas in the blood vessels outside of it. They have also been described as being present in thrombi of the larger branches of the portal veins (Bartlett).

In large amebic abscess of the liver, changes other than differences in size appear. Beyond the inner zone of necrosis, which resembles the corresponding layer of the small lesion, may be seen a capsule that Howard and Hoover described as a broad band of fibrous tissue, poor in nuclei and containing small capillaries. This capsule may be incomplete, and may show, in places, the advancing destructive changes of the small lesions (Councilman and Lafleur). Beyond the abscess, distortion of hepatic tissue by pressure has been described (Rogers [96]), although

114. Koch, Robert, and Gaffky, Georg: Bericht über die Thätigkeit der zur Erforschung der Cholera im Jahre 1883 nach Egypten und Indien entsandten Kommission, Arb. a. d. k. Gsndhtsamte. **3**:1, 1887.

a narrow surrounding border of congestion may be present (Councilman and Lafleur). Amebas are usually present in the necrotic wall of the large cavity (Councilman and Lafleur, Howard and Hoover), but they may be absent from the purulent content (Kuenen). Howard and Hoover described them in the necrotic tissue of the wall of the cavity but not in or beyond the fibrous tissue of the wall or in the deeper capillaries and veins. Councilman and Lafleur were of the opinion that *Endameba histolytica* is not usually found deeper than the necrotic layer, but occasionally they found the organisms in the dilated capillaries at the border.

Bacteria in Amebic Abscess of the Liver.—That the amebic abscess of the liver may be due to the unaided action of *Endameba histolytica* is indicated by the failure to find bacteria in the content of the abscess or in the wall in about half of the cases (Kartulis,[86] Strong and Musgrave, Strong, Knowles). Rogers [115] found bacteria absent from hepatic lesions in half of the cases studied at necropsy and in 86 per cent of those examined at the time of the first operative puncture. Bacteria are present most frequently in the large lesions (Councilman and Lafleur), and Kuenen ascribed to the presence of bacteria the formation of the fibrous capsule in such lesions.

Origin of Amebic Abscess of the Liver.—It is generally agreed that amebic abscess of the liver arises secondarily to the ulcerative process in the bowel (Kartulis, Councilman and Lafleur, Howard and Hoover, Harris,[98] Rogers,[101] and others), even when evidence of amebic intestinal ulceration cannot be demonstrated (Kuenen). Howard and Hoover believed that abscess of the liver was more likely to develop in the chronic cases of amebic dysentery than in the acute cases, although Musgrave in his study of fifty chronic and almost symptomless cases disclosed abscess of the liver in only four. In four cases of multiple hepatic abscess, Kuenen found associated gangrenous intestinal changes in all.

In the attempt to explain the means by which *Endameba histolytica* is transported from the intestinal lesions to the liver, speculation, based on but scant evidence, largely favors the idea that the blood stream coursing by way of the portal system is the carrier of the infection (Kartulis,[86] Harris,[98] Rogers,[96] Kuenen, Strong, Hutchinson, Knowles). Councilman and Lafleur found amebas in the peritoneal exudate in two cases, in one of which intestinal perforation had not occurred, and they believed that the flow of lymph in the peritoneum might transport the amebas across the abdominal cavity to the liver, which the amebas could then attack from the surface. It seemed to them likely, however, that multiple hepatic abscesses could be explained best by assuming an

115. Rogers (footnote 111, second reference).

embolic process in the portal system. In 1902 and 1903, Rogers [101] favored the idea of the peritoneal lymph current carrying the amebas to the liver, but he believed later [96] (1913) that this mode of transportation must be rare. Boyers, Kofoid and Swezy [116] claimed to have found *Endameba histolytica* in material obtained by duodenal tube.

Generalized Hepatic Changes in Amebiasis.—More or less generalized hepatic changes in cases of amebiasis have been described, both changes accompanying hepatic abscess and changes occurring in its absence. Councilman and Lafleur found the liver larger than normal or, as frequently, smaller. They described degeneration about the intralobular veins, hyperplasia of the bile ducts and portal fibrosis. Similar changes were described by Strong. Howard and Hoover found the portal regions prominent and fibrotic. In the absence of hepatic abscess, Bartlett found swelling and fatty changes in the central zone, infiltration of the connective tissue of the portal system with lymphocytes and plasma cells, increased portal fibrosis and occasional parenchymatous necrosis, accompanied by infiltration with pus cells. Rogers [96] expressed the belief that the frequent development of hepatic cirrhosis in India might be due to toxic irritation having its origin in intestinal amebiasis.

Amebic Abscess of the Lung.—Amebic abscess of the lung appears with less frequency than that of the liver and is usually (Clark, Knowles), if not always, due to direct extension of the hepatic lesion into the pulmonary tissue (Councilman and Lafleur, Rogers [96]). The lower lobe of the right lung is most commonly involved (Councilman and Lafleur), although Rogers [96] described an involvement of the lower lobe of the left lung. Even when a communication between the amebic abscess of the liver and that of the lung was not readily demonstrated, Rogers [96] felt that it could, nevertheless, be shown to exist. In one of his cases of abscess of the lung, the hepatic process producing it was so small and so near the upper surface of the liver that the thin intervening wall had been destroyed, leaving a superficial cup-shaped depression in the surface of the liver, easily leading to the impression that the hepatic change was secondary to the larger pulmonary abscess, rather than the reverse.

Councilman and Lafleur described the involved pulmonary lobe as solid, edematous, white and opaque or transparent. The alveoli were small and filled with fibrin, and there was an ingrowth of connective tissue; the epithelial cells were cubical and resembled secreting cells. The bronchi were thick and filled with erythrocytes, whereas some contained fibrin and pus. Connective tissue grew into them from the walls.

116. Boyers, L. M.; Kofoid, C. A., and Swezy, Olive: Chronic Human Amoebiasis: A Review of the Diagnosis and Treatment on the Basis of Encystment in the Liver Area, J. A. M. A. **85**:1441, 1925.

The cavities were usually empty, and were lined by an opaque, necrotic coat projecting irregularly into the cavity, with here and there a broken layer of connective tissue. In places were found well preserved elastic fibers and some large round cells resembling amebas. The content of the cavity was composed of granular detritus, lymphocytes, fat droplets and amebas. Here, again, a well developed protective membrane or abscess wall was absent.

Amebic Abscess of the Brain.—Amebic abscess of the brain is exceedingly rare. Knowles was able to find reports of only 50 or 60 cases as recently as 1928. During the study of 384 cases of abscess of the liver, Kartulis [88] observed but 11 cases of abscess of the brain, an incidence of 0.3 per cent. Of these, 10 were associated with the hepatic lesion. Not only is the process in the brain usually accompanied by an amebic abscess of the liver (Kartulis,[88] Legrand,[117] Knowles), but it has frequently appeared to develop following operative drainage of the latter (Kartulis,[88] Armitage,[118] Clark). In 1912, Legrand reviewed the literature on the subject and reported 48 cases of amebic abscess of the brain appearing up to that time. The lesion ranged from 2 to 6 cm. in diameter. All but 3 were in male patients, and all but 10 showed the presence of *Endameba histolytica*. Legrand found the distribution of the abscesses of the brain to be as follows: 12 solitary abscesses in the right cerebrum, 6 bilateral cerebral abscesses, 6 abscesses opening into the lateral ventricles, 1 abscess in the left cerebellar lobe and 10 indeterminate abscesses.

The puslike content of the amebic abscess of the brain has been described as similar to that of the amebic process in the liver (Strong), grumous and reddish (Armitage) or thick and greenish yellow (Sitsen [119]). It is composed of degenerating neuroglia, nerve and myelin fibers, erythrocytes and pus cells (Armitage). Amebas may be present in the content of the abscess (Kartulis,[88] Legrand) and in the wall of the cavity (Sitsen). Bacteria are usually absent (Strong).

The wall of the abscess of the brain does not contain a membrane or sac (Armitage), but appears to result from progressive ulcerative necrosis (Legrand). It is ragged, shows projecting and thrombosed blood vessels and remnants of tissue, and is surrounded by an areola of punctate hemorrhages, dilated blood vessels and lymphocytic infiltration (Legrand). Amebas are in the necrotic wall (Legrand, Sitsen), as well as in the deeper tissue (Legrand).

Viereck described a case of multiple, superficial, flat hemorrhagic lesions about 2 cm. in diameter. They appeared in the frontal region

117. Legrand, quoted by Armitage (footnote 118).

118. Armitage, F. L.: Amoebic Abscess of the Brain, with Notes on a Case Following Amoebic Abscess of the Liver, J. Trop. Med. **22**: 69, 1919.

119. Sitsen, A. E., quoted by Armitage (footnote 118).

at the base of the brain, in the corpus striatum and in the right occipital lobe just under the surface. Organisms found in these lesions were identified by Schaudinn as *Endameba histolytica*.

Legrand described the dura as being more or less engorged with blood, but rarely adherent to the underlying lesions. The arachnoid was clear, and spinal puncture gave negative results. Legrand found the pia mater sometimes healthy and sometimes edematous; or if the abscess was near the surface of the brain, the pia might be grayish, red or violet, swollen and projecting. Occasionally, the convolutions above the lesions were flat and diffusely red; at times, amebas were present in small numbers on the surface of the brain in the region of the inflammatory area.

It is highly probable that *Endameba histolytica* is transported to the brain by way of the blood stream (Kartulis,[88] Viereck, Sitsen, Knowles). Sitsen described a case of abscess of the brain in which an accompanying abscess of the liver communicated directly with the vena cava. Draining an amebic abscess of the liver appears to be a frequent exciting cause of cerebral abscess (Kartulis,[88] Armitage, Clark). At necropsy in cases of amebic abscess of the liver, the hepatic process has been described as "healing" (Kartulis,[88] Sitsen).

Amebic Abscess of the Spleen.—Only two cases of amebic abscess of the spleen have come to my attention (Maxwell,[120] Rogers [96]). Both were clinical, only; in both motile amebas were shown in the aspirated fluid and in both the patients were cured, one patient by aspiration combined with the use of emetine. Maxwell expressed the belief that in his case the spleen was invaded directly by way of the splenic flexure of the colon. Bartlett did not find splenic changes in cases of uncomplicated intestinal amebiasis.

Other Complications of Amebiasis.—Complications of amebiasis beyond those involving the liver, brain and spleen consist largely of changes resulting from intestinal perforation of amebic ulcers, extension of hepatic abscesses into adjoining structures or rupture into neighboring cavities of the body.

Kartulis [113] described empyema of the pleural cavity, with direct communication between the pleural cavity and an amebic abscess of the liver. In the case of Howard and Hoover, a case of thoracic empyema of the right side, communication between the pleural cavity and the abscess of the liver was by means of an opening through the diaphragm large enough to admit the hand. The lung was flattened and airless, whereas the pleura was thick, covered with a layer of fibrin and infiltrated with lymphocytes and pus cells. On and in the exudate,

120. Maxwell, J. P.: Two Rare Cases from Fukien Province, South China, Tr. Roy. Soc. Trop. Med. & Hyg. **2**:289, 1909.

superficially, were found a few scattered amebas. They were also fairly numerous in the fibrinous exudate within the inflamed pericardial sac. Rogers [96] found hepatic abscess communicating with the pleural cavity on each side, with the stomach, with the stomach and the pericardium, and with the omental bursa. Lesions of the right lobe were found opening into the right colonic flexure, the cecum, the duodenum, the pericardium, the inferior vena cava and the general peritoneal cavity. Kuenen reported retroperitoneal rupture of a hepatic abscess, and Musgrave described two cases of abscess of the liver, one of which communicated with the right pleural cavity, the other of which opened into the abdominal cavity.

Councilman and Lafleur described peritonitis arising from amebic ulceration of the bowel in three cases; in one case, the peritonitis was local, and in two cases it was general. The local process occurred without intestinal perforation; the two general processes were due to perforation, and in the peritoneal exudate of the latter amebas were found. Musgrave reported two deaths from perforation of an amebic lesion of the appendix and five from perforation of ulcers of the colon; four of these ulcers were in the cecum and ascending colon and one was in the transverse colon. Kuenen described peritoneal irritation resulting in cases in which the ulcer reached the layer of intestinal muscle, whereas Clark reported peritonitis to be slightly more common with nonperforating lesions. Perforation explained eighteen of thirty-seven cases of peritonitis. Strong mentioned the possibility of amebic cystitis and the possibility of fistulas being attacked by amebas from the deeper process in the liver or bowel, with involvement of the skin surrounding such fistulous tracts. Inflammatory adhesions (Dopter [4]) may lead to intestinal distortion and obstruction (Davidson).

Lesions differing widely from those generally accepted as peculiar to amebiasis and involving tissues remote from the ones usually attacked by *Endameba histolytica* were reported by Warthin,[121] Kofoid [6] and Panayotatou.[122] Warthin's case was that of a young Russian Jew who had had intestinal amebiasis and who died following operative exploration for a suspected abscess of the liver. Intestinal changes were present, which Warthin interpreted as the results of healed amebic lesions, and, in addition, amebas were found in the left epididymis, in the dilated ductuli efferentes and in a few of the dilated seminiferous tubules near the rete. Some of them contained ingested spermatozoa. Kofoid [6] believed that "Ely's second type of arthritis

121. Warthin, A. S.: The Occurrence of Entamoeba Histolytica with Tissue Lesions in the Testis and Epididymis in Chronic Dysentery, J. Infect. Dis. **30:** 559, 1922.

122. Panayotatou, A.: L'amebiase intestinal et ses localisations extra intestinales, Monograph, Paris, Vigot Frères, 1926, p. 1.

deformans" was due to the action of *Endameba histolytica* and identified endamebas in the tissues of the joint by the character of their mitotic figures. He also described "ameba-like" cells in extirpated glands of patients with Hodgkin's disease [108] and later identified them as *Endameba histolytica*. The amebic bronchitis, cystitis, nephritis and mastitis of Panayotatou could not be verified by pathologic examination of tissues, since all of her patients recovered following the use of emetine.

Parenchymatous changes not associated with the presence of *Endameba histolytica* in the tissues involved will not be discussed. They are not peculiar to amebiasis but resemble those of infection and toxemia in general.

AMEBIC LESIONS IN ANIMALS

The experimental production of amebiasis in animals has usually been incidental to the study of *Endameba histolytica* as a protozoon parasite or to attempts to determine its pathogenicity. Too frequently, statements that amebic lesions were present in the intestinal tract of the experimental animal have constituted the sole contribution to the knowledge concerning the pathologic changes produced. Careful, exhaustive studies of amebic lesions produced experimentally have rarely been made; the descriptions of them frequently have contained just enough detail to establish the amebic nature of the lesions. Into experiments in inoculation there have been introduced, also, operative procedures (Sellards and Theiler, Rees [123]) that have of themselves so modified the intestinal changes, at times, as to make it difficult to separate the changes resulting from operation from those due to *Endameba histolytica* acting alone. Commonly, a superficial resemblance between the amebic lesion of man and that of animals has been noted, and only rarely have any essential differences been stressed (Viereck).

Amebiasis in Kittens and Cats.—In kittens and cats, as in man, intestinal ulceration resulting from the action of *Endameba histolytica* is largely restricted to the colon (Kovacs, Quincke and Roos, Kruse and Pasquale,[124] Marchoux and others), with only occasional involvement of the lower part of the ileum (Sellards and Theiler, Boeck and Drobohlav [10]). Generalized changes of the colon have been described (Kovacs, Boeck and Drbohlav,[10] Wagener, Kessel [63]). Regions of localization of the amebic lesions within the colon most frequently specifically mentioned have been the cecum and rectum (Marchoux, Kessel [63]). The rectum has been named as the region most prone to attack (Wenyon,[5] Sellards and Baetjer,[59] Sellards and Leiva,[57]

123. Rees (footnotes 64 and 67).

124. Kruse and Pasquale (footnote 44, first reference).

Wagener). Dale and Dobell thought the upper and the lower third of the colon to be most frequently involved, whereas Boeck and Drbohlav [10] believed the same to be true of the cecum and the sigmoid flexure. In operative ligature of the bowel that has been the site of injection, lesions were always restricted to the bowel above the point of occlusion (Sellards and Theiler, Rees [123]). In these cases, Rees [60] found that the most severe lesions were those that developed in the region of the ileocecal valve.

Intestinal Amebic Lesions of the Cat and Kitten: Experimental amebiasis in cats and kittens frequently produces a superficial lesion of the mucosa of the intestine (Kartulis,[41] Kruse and Pasquale,[124] Dopter,[1] Baetjer and Sellards,[73] Sellards and Leiva,[57] Knowles). Knowles expressed the belief that this was the only intestinal lesion produced in the cat and that deep and circumscribed ulceration did not occur. This was the experience of Kruse and Pasquale.[124] Sellards and Baetjer [59] recognized this lesion as "early," and it was described by them as an "acute hyperemia, congestion and edema of the mucosa and submucosa without ulceration," while Sellards and Leiva [57] believed the superficial lesion to be the one most commonly encountered in the very young animal. The process may be diffuse, without a trace of normal mucosa in the inflamed region (Sellards and Leiva [67]), or more sharply circumscribed (Craig [46]). Mucosal swelling of such a grade as to approach an obstructive lesion was found by Sellards and Baetjer.[59]

In a study of the superficial intestinal lesion of the cat, Kovacs [42] found infiltration of the free surface of the mucosa with round cells, which, in places, reached as deeply as half the thickness of this layer. In regions of greatest cellular infiltration, necrosis occurred, which rarely involved the whole depth of the mucosal layer. Superficial congestion and hemorrhage were present. Changes in the submucosa, vascular congestion and cellular infiltration appeared only below regions of deep mucosal change.

St. John [125] described a small break in the mucosa, which was triangular in shape on cross-section, with the apex of the triangle reaching the deep mucosa or the muscularis mucosae. In this region, the mucosa was destroyed and converted into a débris of changed tissue cells, leukocytes, of which but few were pus cells, with an occasional ameba in the necrotic tissue only. Below this was found edema of the submucosa, with cellular infiltration about the blood vessels.

Continued extension of the superficial ulcerative process may lead to lesions involving the deeper intestinal tissues (Quincke and Roos, Schaudinn, Dopter,[1] Craig,[46] Wenyon,[5] Baetjer and Sellards,[73] Sellards

125. St. John, J. H.: Differential Characteristics of the Amoebae of Man in Culture, Am. J. Trop. Med. **6**:319, 1926.

and Baetjer [59] Dale and Dobell, Boeck and Drbohlav [10] and others) and reaching, at times, the muscle layer (Jürgens,[126] Boeck and Drbohlav [10]). Submucosal extension may outstrip the overlying mucosal lesions, producing an undermined ulcer that is covered in part by mucosa and that may resemble the advanced amebic lesion found in the intestinal tract of man (Craig,[40] Jürgens, Wenyon,[5] Sellards and Baetjer [59]). Local and remote defensive inflammation may surround the deeper lesion (Dopter [4]) with vascular congestion and cellular infiltration (Jürgens). Boeck and Drbohlav [10] described moderate inflammatory reaction about the deep intestinal lesions of the cat, however, with but few pus cells in the irritated regions.

Rees [66] recently described the changes produced in kittens by the operative injection of cultures of *Endameba histolytica* into the cecum, accompanied by ligature of the bowel below the point of inoculation. In one animal, killed ninety hours after inoculation, there was complete destruction of the epithelium lining the colon, with great thickening of the mucosa and submucosa and necrosis of many of the deeper cells. Rees expressed the belief that an early and characteristic change of the intestine of the kitten was widely opened mucosal crypts and increased distention of the goblet cells (see also Hadley [127]). In the latter observation, however, Rees failed to draw a sharp distinction between the lesions presented by animals without intestinal occlusion and those accompanying artificially produced obstruction. Whether these changes occurred in both groups of animals is not clear.

No account of a submucosal lesion unconnected with a lesion of the mucosa, in the cat, such as that noted in descriptions of amebic intestinal ulcers in man, has come to my attention. All observers are agreed that the deeper lesions in this animal results from extension of the mucosal process.

In the ulcerative lesion of the intestine of the cat and kitten, *Endameba histolytica* has been found in the mucus on the inner surface of the bowel (Kovacs), in regions of superficial necrosis and in the necrotic masses (Kovacs, Dopter,[1] Boeck and Drbohlav [10]). Kovacs found amebas in deep necrotic regions, as did Schaudinn, Quincke and Roos and St. John.[125] Kovacs found none beyond the bordering infiltration, although Schaudinn described them in distant, healthy tissue. Jürgens and Wenyon [5] described them in intact crypts of the mucosa and believed the destructive process was initiated there. Dopter,[1] on the other hand, found amebas only in glands the epithelial cells of which had undergone previous change. He [1] and Rees [67] believed the first

126. Jürgens: Die Amöben-Enteritis und ihre Beziehungen zur Dysenterie, Ztschr. f. exper. Path. u. Therap. **4**:769, 1907.

127. Hadley, P. B.: The Part Played by the Goblet cells in Protozoan Infections of the Intestinal Tract, J. M. Research **36**:79, 1917.

attack to be superficial, with simultaneous destruction of the surface epithelium and the interglandular connective tissue. In one cat, Boeck and Drbohlav [10] found *Endameba histolytica* within blood vessels of the submucosa.

Amebic attack on the solitary intestinal lymph follicles occasionally has been observed (Jürgens, Boeck and Drbohlav,[10] Rees [67]). Jürgens expressed the belief that the only intestinal lesion present in amebiasis of the cat might be widespread and deep invasion of these structures.

As in man, amebic invasion of the mesenteric lymph nodes is extremely rare in the cat. Wenyon [5] alone described a mesenteric node filled with large numbers of *Endameba histolytica,* some of which contained digested cells of glands. Simpler changes are not uncommon. Jürgens found them swollen, and Dale and Dobell described them as purulent at times, but amebas were never present in them.

Bacteria have been believed to play an important part in the amebic lesion of the cat, if only as a secondary invader (Wenyon [5]). Sanders wrote of terminal bacteremia, and mentioned the likelihood of earlier bacterial sepsis. Sellards and Baetjer [59] thought that death in the younger animals was more frequently the result of bacterial invasion of the body by way of the amebic lesions of the bowel than the consequence of the amebic process itself. Dale and Dobell believed the death of animals ill with amebiasis was usually due to sepsis, although this view was not based on bacterial studies of the local intestinal lesions nor of distant organs. Rees [66] spoke of the possible importance of bacterial modification of the amebic intestinal process.

Healing of the amebic lesion in the intestinal tract of the cat and the kitten is rare. The older and more resistant cat is more likely to show the chronic and undermined ulcer, and has been known to become a carrier of the infection, remaining free from symptoms of amebiasis (Sellards and Baetjer [59]). The recovery of a cat previously infected with *Endameba histolytica* has been described (Schaudinn, Mayer), and Wagener and Thomson mentioned finding healed intestinal ulcers in a cat previously ill with dysentery.

Abscess of the Liver in Cats.—Amebic abscess of the liver is the only complication of dysentery that has been described as occurring in the cat or the kitten. Sellards and Baetjer [59] believed it developed in the more chronic cases, whereas Marchoux found it associated with ulcerative lesions of the rectum and believed its development to be the rule in animals that lived as long as fifteen days. Sanders found abscesses of the liver in 3 kittens that died of amebic dysentery after twenty, twenty and twelve days, respectively. Of 126 kittens infected experimentally by Mayer (see study 2) later presented abscess of the liver, 1 as early as four days after the appearance of the symptoms of

dysentery, others as late as from two to three weeks. The abscesses may be solitary (Marchoux, Werner, Baetjer and Sellards,[73] Sanders) or, rarely, multiple (Marchoux, Sanders). When they were multiple, Marchoux found them to be small.

Meager descriptions of the amebic abscess of the cat indicate that it is similar to the amebic lesion of man. It was described by Baetjer and Sellards [73] as "more a necrosis than an abscess," and Boeck and Drbohlav [10] observed it to be free from a surrounding inflammatory reaction. Sellards and Baetjer [59] found the content of the abscess to be of such a nature that "none of it could have been aspirated." Amebas are usually present in the hepatic lesion (Marchoux, Werner, Sellards and Baetjer,[59] Dale and Dobell, Mayer, Boeck and Drbohlav,[10] Sanders), whereas bacteria may be present (Marchoux) or absent (Boeck and Drbohlav [10]). Strangely, Mayer observed cysts of *Endameba histolytica* in the content of the abscess in two of his four cases.

Amebiasis in the Dog.—The condition is rare in this animal (see study 2), and few complete descriptions of the intestinal lesions produced by *Endameba histolytica* have appeared in the literature. Yet, interestingly enough, the first experimental lesion in an animal was that produced in the dog. In the colon of one dog experimentally infected with amebiasis Lösch observed intestinal ulcers, in the mucus of which he found amebas similar to those used for the inoculation. Harris [65] described two types of intestinal lesions in experimentally induced amebiasis of the dog: an "acute" and a "chronic" lesion. The acute lesion occupied the summits of the intestinal mucosal folds and began as catarrhal desquamation of the surface cells with later involvement of the basal membrane. Early the mucosal crypts were narrowed, while the epithelial cells lining them seemed to be intact. The mucosa was swollen and hemorrhagic, and the blood vessels and lymph spaces were dilated. Later, the glandular crypts were destroyed down to the submucosa, and amebas were present in the mucosa and in the "exudate." In the mucosa outside the ulcerative process were dilated blood vessels and lymph vessels with their lining epithelium swollen and often desquamated. Below the mucosa, the submucosa was swollen, infiltrated with lymph and erythrocytes, and contained distended blood vessels. In the chronic lesion, the observations were similar to those of the acute lesion, except that more conspicuous submucosal changes appeared; to the cellular infiltration were added mast cells and a few pus cells. Two of the animals had abscesses of the liver. The lesions here were described as small and bordered by hepatic cells only, and there were but slight surrounding changes. In the content of the abscesses was débris, in which could be recognized erythrocytes, pus, hepatic cells and amebas. In a dog dead of spontaneous amebiasis,

Darling [72] found the whole colon the seat of minute, punctiform, red erosions of the mucosa surrounded by swollen, pale yellow mucosa covered with flakes of mucus. Large ulcers were not present. The small, eroded spots were infiltrated with amebas and leukocytes. In regions, the superficial epithelium had been replaced by great masses of amebas, which had effected slight penetration of the mucosa. Amebas were also present in the lower part of the ileum and had invaded the wall of the bowel at one place without having produced a recognizable ulcer.

Amebiasis in the Rabbit.—Two observers reported the production of amebiasis in the rabbit. Huber described the cecum of the affected animal as hard, thick and opaque; the inner surface was red and ulcerated, but was covered in large part by mucosa. This process was confined to the cecum, although the upper third of the colon was inflamed and contained blood-tinged mucus. He found the amebas entering the wall of the bowel by way of the mucosa, which showed but little change. In the submucosa, which was thickened, were cellular débris, leukocytes, dilated blood vessels and amebas. He expressed the belief that the surface defect resulted from the more extensive submucosal process, breaking its way through the mucosa from below. Thomson found amebas invading the mucosa, the submucosa and the circular layer of muscle of the cecum, to which the process was confined. She found *Endameba histolytica* also in the intestinal lymph nodes and lymph channels, as well as within blood vessels and within spaces surrounding them.

Amebiasis in the Guinea-Pig.—The only full description of the rare amebic lesion in the bowel of the guinea-pig is that of Chatton.[81] He found the cecum thick, rigid and contracted, with numerous white spots on the inner surface, which proved to be miliary abscesses. In severe cases he found some slight involvement of the rectum, but did not find true intestinal ulcerative lesions. The cecal mucosa was thickened, cystic and covered with a diphtheroid membrane. Scrapings of this showed much detritus, mononuclear cells and amebas, which, on staining, were recognized as *Endameba histolytica.* The submucosa was greatly thickened and more nearly resembled a spindle cell sarcoma than a region of inflammatory hyperplasia.

Amebiasis in the Rat.—Although the rat has been used frequently in the experimental production of amebiasis and seems susceptible to the disease (Lynch, Brug, Kessel,[128] Chiang), descriptions of the lesions produced are few. Lynch described the process as usually restricted to the cecal portion of the colon. The lesions varied from the typical amebic ulcer to a catarrhal lesion with some superficial erosion of the

128. Kessel (footnote 78, first and second references).

mucosa without gross ulcerative lesions. Cysts of *Endameba histolytica* have been described as occurring in the intestinal content of the infected rat (Lynch, Kessel [129]).

Amebiasis in Other Animals.—Intestinal changes due to amebiasis in other animals will not be considered here. With the exception of the monkey, which has been frequently rejected for use in the production of amebic dysentery because of the likelihood that it may develop the disease spontaneously and the expense of using such animals (Sellards and Leiva,[60] Dobell and Laidlaw), amebic changes produced in animals other than those already considered have been exceedingly rare.

NATURE OF THE ATTACK

In considering the nature of the attack of *Endameba histolytica* on human and animal tissue, wide differences of opinion have been expressed. Schaudinn expressed the belief that destructive changes were largely due to the mechanical action of the hard pseudopodia extruded by the organism. Kartulis [86] favored this explanation at first, but later [87] adhered to the idea that the ameba acted on tissue by means of a proteolytic secretion. This explanation of the action of *Endameba histolytica* seemed more reasonable to Harris,[98] Dopter,[4] Christoffersen, Dobell,[9] Hegner and Taliaferro, James,[130] Knowles and Hutchinson. Some experimental evidence in support of the belief now generally accepted, that *Endameba histolytica* acts by the production of a tissue-destroying enzyme, is that of Wagener and that of Craig.[131] Wagener was able to show that the blood of animals ill a week or more with amebiasis gave a positive precipitin reaction with an antigen prepared from the scrapings of the amebic ulcers of the intestinal tracts of cats. Craig [131] showed that alcoholic extracts of *Endameba histolytica* from cultures presented complement-binding properties and were hemolytic and cytolytic in action. In favor of the mechanical action of *Endameba histolytica*, Hadley presented evidence that a trichomonas of birds may enter the intestinal tissue by way of the goblet cells of the mucosa, and thought, by analogy, that the same might be true of *Endameba histolytica* in the intestinal tract of mammals. Evidence has not been presented to substantiate this belief.

Differences of opinion concerning the pathogenicity of *Endameba histolytica* have appeared. Musgrave found amebic lesions in all of

129. Kessel (footnote 78, second reference).

130. James, W. M.: Some Observations on Intestinal Amoebiasis Due to Infection with Entamoeba Histolytica, United Fruit Company, Med. Dept. **1:** 185, 1927; footnote 105.

131. Craig, C. F.: Observations upon the Hemolytic, Cytolytic and Complement-Binding Properties of Extracts of Endamoeba Histolytica, Am. J. Trop. Med. **7:** 225, 1927.

fifty patients who displayed, during life, few if any of the usual symptoms of amebic dysentery. Dobell [9] believed *Endameba histolytica* was always pathogenic for man, and the work of Kessel [63] indicated that this was probably true. However, he described monkeys harboring *Endameba histolytica,* which seemed to be present in them as harmless parasites. That the same may be true of *Endameba histolytica* in man, also, has been suggested by James,[130] Knowles and others.[132]

The part played by bacteria in amebic lesions has been the subject of controversy. At first, Kartulis [86] held that bacteria were the true cause of the lesions, both intestinal and hepatic, although later he [87] thought that amebas, unassisted, were capable of producing lesions. Woolley and Musgrave and James [133] felt that *Endameba histolytica* did not attack healthy bowel, but initiated lesions only following irritative changes due to other causes, probably bacterial.

Concerning the points or regions of the primary attack of *Endameba histolytica* on the intestinal wall, widely diverging views have been held. That the mucosa was the tissue attacked first was held by Dopter,[4] Kuenen, Christoffersen, Kaufmann and Wenyon.[51] Wenyon [51] expressed the belief that the intact glandular crypts were invaded first, whereas Kuenen and Delafield and Prudden thought the first or principal attack of *Endameba histolytica* was on the mucosal connective tissue. Kofoid [6] expressed the belief that either the epithelial cells or the connective tissue of the mucosa might be attacked first, whereas James [105] found both involved equally. Councilman and Lafleur thought the first intestinal change was that of the submucosa. To reach it, the amebas traversed the mucosa, without changing it appreciably. They expressed the belief that the ulcerative destruction of the mucosa that was seen in the larger lesions was due to the extension of the deeper process into the lumen of the bowel. With this view Kruse and Pasquale,[99] Harris,[98] Rogers [101] and Bartlett also agreed.

METHODS

The amebic lesions for this study were produced by introducing motile forms of *Endameba histolytica* from the stools of man into the intestinal tracts of kittens by rectal injection, by injecting ameba-containing stools of kittens thus infected into others in the same manner, and by the injection of *Endameba histolytica* from cultures directly into the cecum of kittens following laparotomy (see study 2). In some of the last group, the bowel was ligated near the rectum at the time of inoculation, whereas some received the cecal injection only. Two of the former group of kittens and one of the latter became infected with *Endameba*

132. Knowles, R.; Das Gupta, B. M.; Gupta, A. K. D., and Gupta, Umapati: The Treatment of Intestinal Amoebiasis: An Analysis of Results, and a Review of the Literature, Indian M. Gaz. **63**:455, 1928.

133. James (footnote 130, first reference).

histolytica, grown on the medium of Boeck and Drbohlav,[10] to which rice starch had been added as recommended by Dobell and Laidlaw (see study 1).

To prevent the development of intestinal postmortem changes, every animal, that, judged by its actions, seemed about to die soon was killed. As quickly as possible after death, within five minutes, the tissues to be examined were placed in Schaudinn's fixative solution, and, after being sectioned, were stained with iron-hematoxylin and eosin. Some of the kittens used in the beginning of this work were killed as soon as it was determined by an examination of the stool that infection was probably present. This was done so that the earliest amebic lesion might be studied. Later, others were permitted to live until it seemed that they were about to die of the infection. It was hoped that an abscess of the liver might develop in one of the animals. However, none developed, although four kittens lived from six to eleven days following the development of dysentery.

Only one kitten with amebic dysentery died of the infection. This animal was young, and amebas had been present in the stool less than twenty-four hours following an incubation period of one day. Postmortem changes here were so pronounced that it was with difficulty that a diagnosis of amebiasis could be made from an examination of the intestinal tract. My experience with this animal and with others subjected to necropsy as early as one hour after death makes me feel that any delay in obtaining and fixing intestinal tissue after death may result in definite postmortem changes, at least so far as the superficial mucosal epithelium and the amebas are concerned.

RESULTS AND OBSERVATIONS

Of the nine kittens in which intestinal lesions resulted from the rectal injection of stools of human beings or of animals that contained motile forms of *Endameba histolytica,* four showed amebic lesions throughout the colon. In one of these, cecal involvement was most pronounced, whereas, in two, the most conspicuous changes were in the rectum. Of animals presenting less extensive involvement of the colon, one showed many small cecal ulcers, associated with similar processes in the rectum, the remainder of the bowel being free. In three of four older kittens, about half grown, lesions were restricted to the rectum; in the fourth there were small ulcers throughout the colon and more conspicuous lesions in the rectum. When lesions were noted throughout the colon, only small ulcers were found in the middle portion of the bowel. In none of these kittens was there amebic involvement of the ileum.

In two kittens infected by the operative cecal injection of *Endameba histolytica* from cultures, in which intestinal obstruction had been produced artificially, ulceration of the colon was not evident to the unaided eye, although later histologic examination revealed almost complete amebic destruction of the superficial portion of the mucosa throughout the region. In one animal, similarly inoculated with *Endameba histolytica* from cultures, but without ligation of the rectum, there developed in the cecum many superficial amebic ulcers, which decreased in size

and numbers as the middle portion of the colon was approached. Beyond the middle portion of the colon, lesions were not seen.

Early Amebic Lesions in Kittens.—Kitten 28, about a third grown and not previously used experimentally, was killed and examined twenty-four hours after the onset of dysenteric symptoms, which were accompanied by the appearance of *Endameba histolytica* in the stools. There was generalized involvement of the colon with superficial ulcers varying in size from those just visible to the unaided eye to lesions 1 or 2 cm. in diameter. For study by serial section, there was selected a very small isolated ulcer of the middle portion of the colon. It was the smallest lesion recognized as ulcerative that was far enough removed from the other lesions to be surrounded by a moderately wide margin of normal

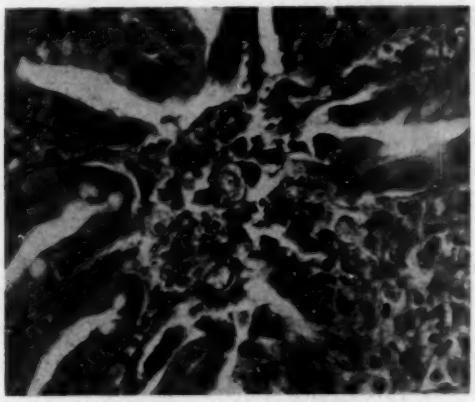


Fig. 5.—The earliest intestinal lesion of kitten 28 (serial section); × 350. Three amebas are in the field, two with nuclei showing. The reaction in tissue is limited.

looking mucosa. In the sections of this tissue, cut and mounted serially, there appeared, not only the macroscopic ulcer chosen originally for study, but several other ulcers, the smallest of which was included in fifteen sections each of which was 8 micromillimeters thick.

This ulcer occupied the depth of a crease in the mucosa [134] and was so sectioned that the adjacent mucosal glandular crypts were cut trans-

134. A careful description of the configuration of the mucosa of the colon of the cat has not come to my attention. Certainly, in the young cat, the saccules, haustra, resulting from the action of the longitudinally placed taeniae coli are very inconspicuous. In the empty bowel there appear, however, mucosal folds or rugae which, in great part, assume a direction transverse to the longitudinal diameter of the bowel. Although roughly transverse in direction, three or more such folds may meet to produce a crater-like pocket, as well as the commoner groove-shaped crease. It is not unlikely, therefore, as seem at times to be the case, that the ameba may initiate changes in this minute circular cavity, as well as in the depths of the longer creases between rugae.

versely or obliquely (fig. 5). Although the lesion was surrounded by mucosa and appeared to occupy a position below the mucosal surface, study of the sections on either side showed that the process was actually limited to the surface epithelium at the bottom of a mucosal crevice, microscopic in size. The small central area of necrosis was composed largely of small cells (lymphocytes?) with small, deeply staining nuclei and a few amebas, not more than two or three of the latter to each section (fig. 5). In one wall of the lesion, glandular crypts bordering the exudate contained shrunken cells with pyknotic nuclei on the sides of the crypts in contact with the central necrotic area, whereas cells of

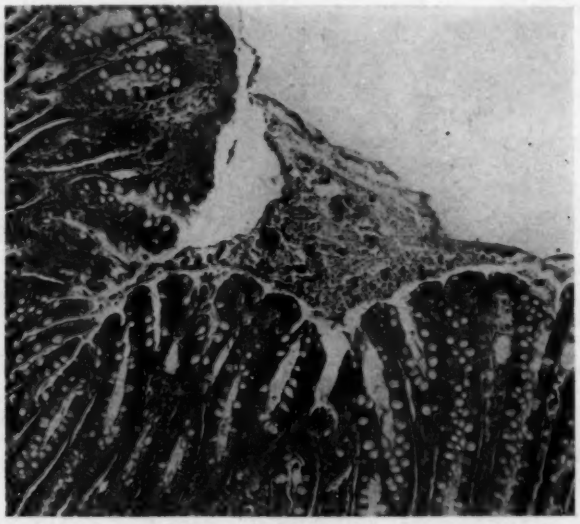


Fig. 6.—Early amebic lesion in the middle portion of the colon of kitten 28 (serial section) showing invasion of the depth of a mucosal crease; × 100.

normal appearance were found in the same glands no farther away than a fraction of the diameter of a mucosal crypt. Goblet cells were visible in a mucosal crypt directly on the exudate. In the opposite mucosal wall were more marked changes; namely, thickened interglandular connective tissue and infiltration of this with cells, mostly lymphocytic. This inflammatory reaction was extremely limited and extended for but a portion of the thickness of the mucosa in any direction, whereas epithelial and connective tissue cells were equally involved in the process. Amebic invasion of unchanged tissue or glandular crypts was not evident. In appearance, the tissue changes seemed to result from the action of a lytic substance, local in its extent, but destructive, nevertheless, out of all proportion to the number of amebas present.

A second and larger amebic ulcer, still microscopic in size, was disclosed by the same serial sections. It showed clearly the tendency for amebic lesions, at least in the middle portion of the colon, to begin in grooves produced by normal mucosal folds (fig. 6). A section near the margin of this ulcer suggested an early lesion, with the amount of change so slight as to raise the question whether a lesion was present, until it was examined under higher magnification (fig. 7). Further study of the sections including this ulcer showed that, although recent, it was far more advanced than the first lesion described. There was more destruction of tissue and amebas were present in the exudate and

Fig. 7.—The area indicated in figure 6, magnified five hundred times. One ameba with nucleus is in focus. One wall shows change in staining reaction of epithelial cells, with slight beginning destruction.

in the necrotic tissue in larger numbers, and cellular infiltration was more pronounced and more widespread. At one point, five amebas were seen to occupy a mucosal lymphatic space that still was lined, in part, by what appeared to be intact endothelium (fig. 8). Here, again, the attack of the amebas seemed to be by means of a lytic secretion that involved epithelial cells and connective tissue equally, and without the invasion of unchanged tissue or glandular crypts by the amebas. Infiltration of the tissue immediately surrounding the area of attack was slight, whereas just below the ulcer and between it and the muscularis mucosae were column-like portions of interstitial tissue showing marked

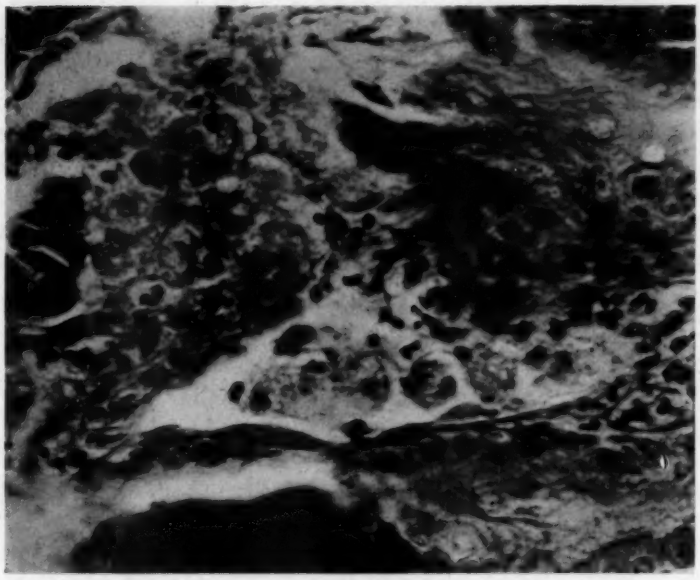


Fig. 8.—A deeper section of the ulcer pictured in figure 6, showing five amebas within a mucosal space lined with endothelium; × 500. Other amebas in changed tissue are surrounded by cellular infiltration.

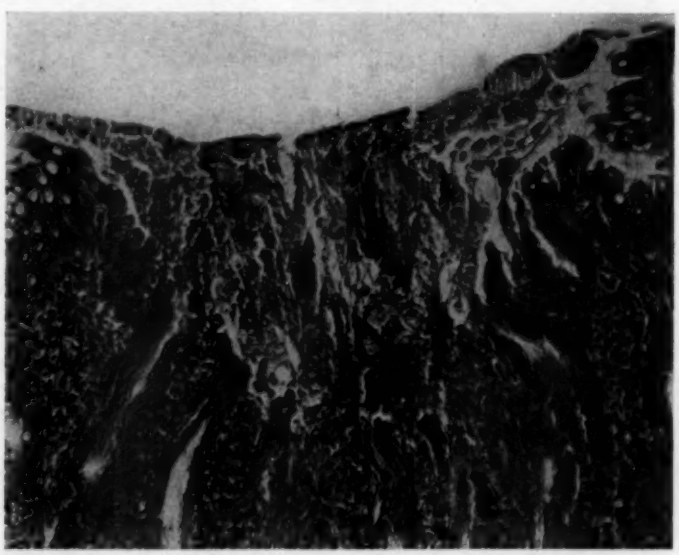


Fig. 9.—Middle section of an ulcer, showing occlusion of crypts of mucosal glands at their juncture with the necrotic tissue; × 150. It is not evident in this section that the attack was determined by a mucosal crease.

infiltration with lymphocytes. In less degree, the latter change sometimes occurred in portions of the bowel that were free from lesions, and in the intestines of cats in which there were no amebic lesions. Surrounding the lesion was about the degree of production of mucus commonly seen in the colons of kittens that are free from demonstrable lesions of any sort. Only at the point of amebic attack was there no production of mucus.

Reconstruction of a third ulcer disclosed by this series of sections showed it to be bluntly cone-shaped, with the circular base at the free border of the mucosa, and the rounded apex approaching, but not reaching, the muscularis mucosae. The necrotic core, still in place, was composed of structureless, granular débris in which were recognizable amebas and erythrocytes. The study of sections through one edge of the ulcer showed that it, too, had its beginning in a mucosal fold. This impression would not have been gained, however, by an examination of sections from the center of the lesion alone or from the opposite margin (fig. 9). The line of demarcation between the necrotic center and the surrounding tissue was not sharp. The floor of the ulcer was ragged. Destructive changes increased gradually as the lesion was approached, with cellular infiltration so marked that the only recognizable tissue present at the necrotic border was an occasional, loosened, shrunken and deeply staining epithelial cell. The infiltration was largely lymphocytic, was below the ulcer rather than around it, and so compressed and distorted the mucosal crypts that near the points where they entered the necrotic zone they appeared occluded. Production of mucus in the mucosa surrounding the ulcer was normal and persisted to the margin of the ulcer. Goblet cells were entirely absent in these crypts; only the superficial portion of the mucosa was destroyed by the ulceration. No amebas were in the glandular crypts or in tissue outside the area of necrosis. In this lesion, extending but little deeper than half the thickness of the mucosa, submucosal changes were absent.

Serial sections of the larger lesion originally selected for macroscopic study showed it to extend more widely over the mucosal surface, although its depth was but little greater than half the thickness of the mucosa. The necrotic tissue, more a cap than a corklike core, flowed out over the mucosa at one side of the lesion as a thin, ameba-containing cover. Below the central necrotic mass and below the exudate extending over the mucosa, there were marked lymphocytic infiltration of the interstitial tissue of the mucosa and absence of goblet cells. Beneath the thin, ameba-containing sheet there was patchy destruction of the most superficial epithelial cells only. In the region of the ulcer and in the depths of the necrotic tissue were amebas in large numbers. Following the sections from the margin of the ulcer toward its center, one found that the mucosal crypts, closed in their more superficial portions

by the surrounding cellular infiltration, finally opened directly into the central exudate as the destructive process approached their more deeply placed and slightly expanded blind ends. Thus it appeared that amebas might enter mucosal crypts after the ulcerative process had reached a depth a little greater than half the thickness of the mucosa (fig. 10). Although there usually were marked changes in the invaded crypts, with loosened and shrunken epithelial cells showing modified staining reactions (fig. 11 *A*), amebas occasionally were found in the depths of glands that showed but little local change other than the absence of goblet cells (fig. 11 *B*). In all instances, however, it was found that the invaded crypts, appearing but little changed in their deeper portions, were but remnants of glands destroyed superficially by the ulcerative process. In all other particulars, this larger lesion corresponded with those already described.

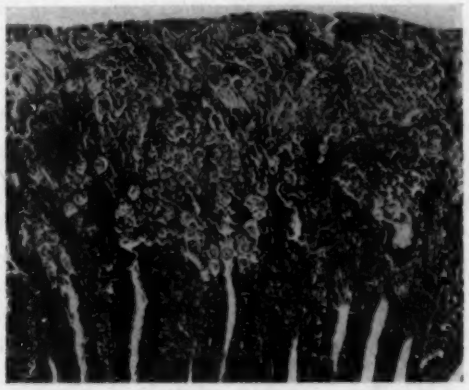
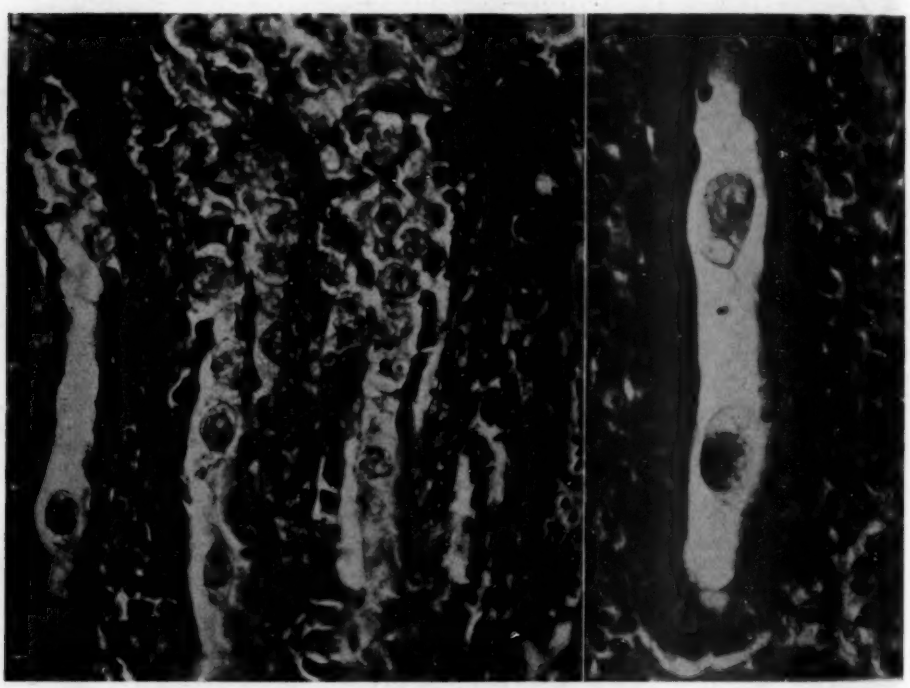


Fig. 10.—Larger amebic ulcer in the middle portion of the colon of kitten 28, showing necrosis of about half the depth of the mucosa; × 100. A few glands are seen to open into the necrotic tissue.

In this kitten there was no involvement of the solitary lymph follicles in the amebic process and no amebas were found in the mesenteric lymph nodes draining the colon.

Kitten 26, previously inoculated with material from the stool of a human being containing *Endameba histolytica* (see study 2), was infected following rectal injection of the dysenteric stool of the first kitten. Three days later, on the first day that symptoms of infection were present and the stool was found to contain *Endameba histolytica,* the kitten was killed and examined. The lesions were small, from 1 to 3 mm. in diameter, superficial and restricted to the cecum. There was superficial involvement of the mucosa, in the natural creases, as well as at the summits, of mucosal folds. Below the destroyed surface the mucosa was markedly infiltrated with lymphocytes and pus cells; in the same region vascular congestion was evident, and the lymph spaces were

filled with lymphocytes and pus cells. Some portions of the bowel were covered with heavy sheets of exudate containing amebas, erythrocytes, detritus and fibrin-like threads, below which there was patchy destruction of the surface epithelium only (fig. 12). In the mucosa involved in the ulcerative or exudative process, production of mucus was absent (fig. 12), although it was normal or increased in regions free from amebas (fig. 13). Moderate lymphocytic infiltration of the superficial portion of the submucosa immediately below the destructive mucosal lesions was observed.



A B

Fig. 11.—*A*, a deeper section of the ulcer shown in figure 10; × 350. There is amebic invasion of the mucosa crypts, with destruction of the epithelial cells lining them. Several amebas contain erythrocytes. *B*, mucosa below the ulcer pictured in *A* and in figure 10, showing two amebas in a normal-appearing mucosal crypt; × 500. A mitotic figure is shown in the epithelium adjacent to one of the amebas.

Similar results were presented by kitten 32, killed the day after the appearance of amebas in the stool, except that involvement of the rectum, as well as of the cecum, was present, and that in the rectal lesions there was a greater degree of lymphocytic infiltration of the involved mucosa than was shown by similar lesions in the cecum.

Fig. 12.—A superficial lesion of the colon of kitten *26*, showing a fibrin-like exudate, containing amebas, which cover the mucosa and two areas of superficial destruction. The crypts are closed near the surface; the mucosa is infiltrated, and goblet cells are almost entirely absent; × 75.

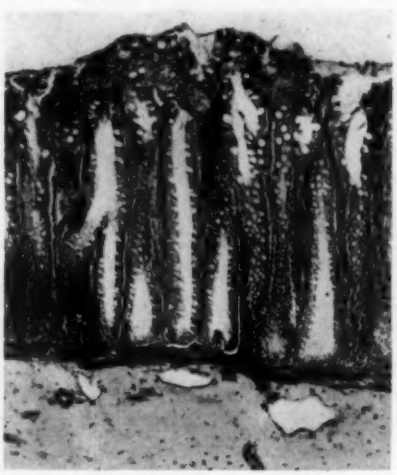
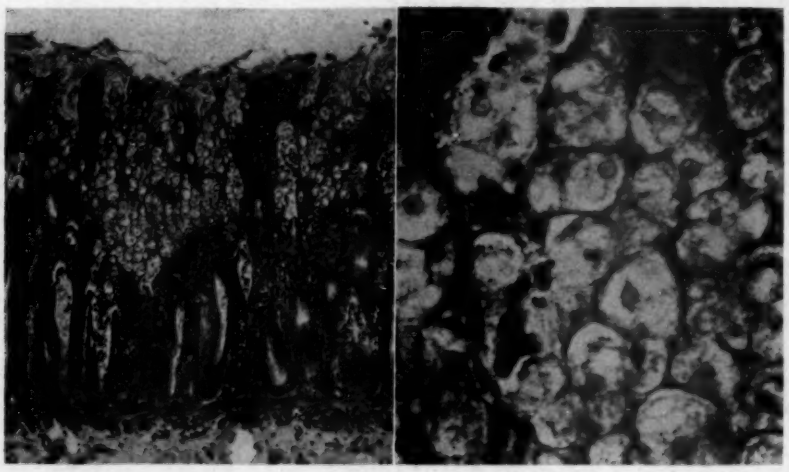


Fig. 13.—Mucosa of the colon of kitten *26*, away from an amebic lesion, showing increased production of mucus; × 75.

Kitten 14, previously used experimentally, was operated on under ether anesthesia and motile forms of *Endameba histolytica* from a starch-containing medium were introduced into the cecum by means of a hypodermic needle (see study 2). The rectum of this animal was not occluded, and at the end of four days, when the animal was killed, examination of the stools showed amebas. There were small, superficial ulcers, restricted to the cecal half of the colon. In the middle portion of the colon was found, on section, one wedge-shaped lesion of the mucosa reaching about two thirds of the distance to the muscularis mucosae, but without loss of the necrotic tissue (fig. 14 *A*). In the deeper portion of the ulcer were great masses of amebas (fig. 14 *B*), a few of which had invaded glandular crypts (fig. 14 *A*). The cecal



A B

Fig. 14.—*A*, colonic ulcer in kitten 14, showing invasion of mucosa by great masses of amebas and marked cellular infiltration of mucosa below the necrotic area; × 100. *B*, the area indicated in *A*, showing morphologic details in the mass of amebas; × 500.

lesions were similar to this and all were free from submucosal infiltration.

In four kittens, lesions developed in layers deeper than the mucosa. These animals were older than those used previously, being about half grown. On the same day all received rectal injections of the ameba-containing stool of a patient who had active symptoms of dysentery. All became infected after an incubation period of from six to nine days, and were killed six to eleven days later, when it seemed that they were not likely to live much longer. In all, large, deep, sloughing ulcers of the rectum were found, and in three the amebic lesions were restricted to this region. In the animals with rectal lesions only, the

colon above the ulcers was packed with formed material that varied from a putty-like to a chalklike hardness. But little moisture was present in the portion of the bowel containing the solid content, and the solid content was removed from the wall of the bowel with difficulty. The kitten with lesions in the upper portion of the colon had an intestinal content that was small and fluid. The deep rectal lesions were similar in all four kittens. The wall of the bowel in the region involved was greatly thickened, and section showed that this was due largely to changes involving the submucosa. The ulcers were from 2 to 3 cm. in diameter, crater-like and denuded of mucosa. The greatly thickened necrotic submucosa was in place in part, although the destruc-

Fig. 15.—A rectal lesion in kitten 37, showing amebic destruction of the greatly thickened submucosa and undermining of the mucosa; × 25.

tive changes reached the circular muscle of the wall of the bowel and extended laterally beneath the mucosa, surrounding the central defect, thus producing at least potentially, the undermined lesion so frequently described as typical of the amebic ulcer of man (fig. 15). Surrounding the necrotic submucosa, which was so changed as to show no recognizable elements other than amebas and the occasional shadows of blood vessels, there appeared a rough, fibrin-like border in which were embedded lymphocytes and pus cells, and changed, but distinguishable, tissue cells. Extending widely beyond the border of the deep portion of the lesion and deeply into the muscle layers of the bowel were numerous invading cells, many of them polymorphonuclear leukocytes.

In this region were dilated lymph spaces and blood vessels filled with erythrocytes and leukocytes. In the walls of the blood vessels and surrounding them was a region heavily infiltrated with leukocytes, the greater numbers of which were pus cells. The mucosa surrounding the ulcer was the site of patchy surface involvement; mucosal crypts were distorted and destroyed, cellular infiltration was present and amebas were found in great masses; the amebas were found in the deeper necrotic zones, centrally placed, rather than at the margins, occasionally within an involved solitary lymph follicle, but not in tissue beyond the region of complete necrosis. Amebas were not present in any of the mesenteric lymph nodes draining the rectum or colon.

Kitten 8 was anesthetized with ether, the abdomen was opened and an injection of *Endameba histolytica* from culture (strain H) was made into the cecum with a needle. At the same time, the colon was ligated in the region of the rectum. This animal had been used experimentally before, but was free from symptoms at the time of the operative inoculation, and the stool, examined just before, had not contained amebas. Two days later the kitten was able to walk around, but was evidently sick. It was killed, and necropsy was performed at once. Old lesions were not found to suggest that the infection might have arisen from an inoculation other than the last one. The abdominal wound had healed without suppuration; the omentum was glued lightly to the posterior portion of the abdominal incision, but fluid was not present in the peritoneal cavity. The rectal ligature was in place, and the bowel was occluded at this point, and, above this, the whole of the colon was so enormously distended by a content of fluid and gas that it hardly seemed possible that there could have been room for it in the abdominal cavity. The distention reached as high as the lower 10 cm. of the lower part of the ileum, and manipulation revealed that the ileocecal valve was widely open. The lymph nodes along the colon and the lower part of the ileum were large, pale and soft, as if edematous. When the bowel was opened, it was found filled with a thick, brownish fluid which extended up the ileum for 10 cm. and which was teeming with amebas. The inner wall of the colon was covered with a thin, mucoid exudate, but ulceration was not visible to the unaided eye. The lower part of the ileum presented a similar appearance, except that here the exudate was in small patches, whereas one area, about 1 cm. in diameter, looked like a minute mucosal hemorrhagic infiltration.

Besides the studies of the intestinal tract and of other organs of this animal, serial sections of the dotlike hemorrhagic lesion of the ileum were made and of an area of the middle portion of the colon, with a mesenteric lymph node adjacent to it. The ileal lesion proved to be an amebic invasion of a solitary follicle. The follicle had been entered by way of its tip, which projected into the ileum of the bowel

(fig. 16), although sections taken near the edge of the lesion showed the invaded follicle covered by relatively normal and intact mucosa (fig. 17). A single section of this small lesion might have failed to show that the invasion of the deeper tissue was by way of the mucosa and might have led to the belief that the amebas reached the depth of the follicle without injury to the overlying mucosal layer.

The nature of the amebic involvement of the solitary follicle was that of widespread necrosis, with destruction of the whole of the interior of the follicle by amebas, which occupied the necrotic abscess-

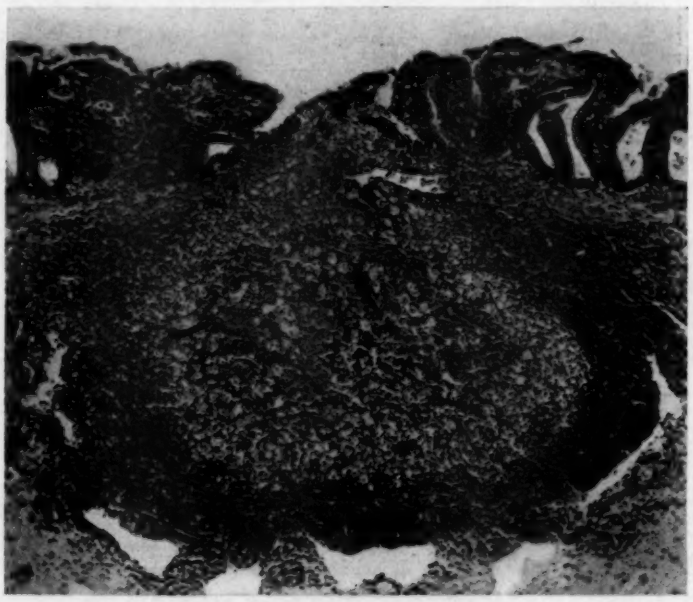


Fig. 16.—A central section of a solitary follicle in the lower portion of the ileum of kitten 8, showing the amebic invasion from the mucosal surface, and great central follicular destruction, with amebas present in large numbers; × 75.

like detritus in great numbers. They did not extend into the unchanged surrounding tissue and were not found outside the follicular limits.

In the ileum, beyond the involved follicle, were many small, superficial areas of mucosal destruction. In some of these, amebas occupied the depths of crypts relatively normal in appearance. The connective tissue of the villi, the interglandular areas and the lymph spaces in the same regions were infiltrated with lymphocytes. The dilated lymph spaces of the submucosa and the tissue surrounding them contained leukocytes, which were mostly mononuclear.

In the colon, from the ileocecal valve to the rectum, were lesions that in their extent and degree of destruction of tissue far outstripped any

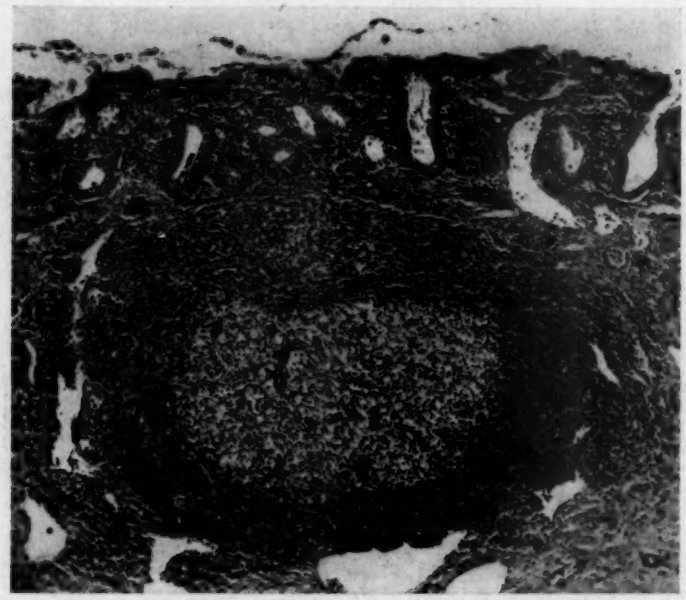
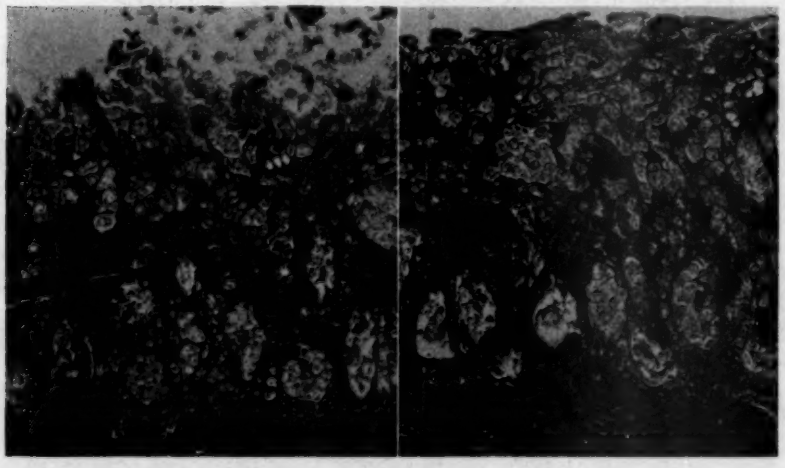


Fig. 17.—A section near the edge of the follicle shown in figure 16; × 75. The destroyed center of the follicle apparently is covered by relatively intact mucosa.



A B

Fig. 18.—*A*, the colon of kitten 8, showing the severe nature of the destructive process in the presence of intestinal obstruction; × 100. *B*, another portion of the colon, showing marked dilatation, invasion and destruction of mucosal crypts, with leukocytic infiltration of the muscularis mucosae and submucosa; × 100.

amebic lesions observed in animals in which operative occlusion of the bowel was not present. It might well be said that there was no ulceration in the usual sense, since the bowel throughout presented one unbroken expanse of mucosal invasion and destruction (figs. 18 *B* and 19). Almost no areas of mucosa remained free from amebic attack, and all showed evidences of irritation. Where the mucosa was involved in the amebic process, marked changes in it occurred. Great masses of amebas were present in all parts of it, in the superficial necrotic portions and in the deeper, dilated and greatly changed mucosal crypts (fig. 18).

Fig. 19.—A solitary follicle in the colon of kitten 8, showing the amebic invasion of the follicle by way of the mucosal surface, with marked central amebic necrosis; × 100.

Where these were recognizable, usually in their deeper parts only, the lining epithelial cells were flat and small, with deeply staining cytoplasm and pyknotic nuclei, or they had fallen into the dilated crypt, where they appeared as deeply staining fragments. Some dilated crypts were recognizable only by their shape, since they were not lined by epithelium and did not contain it within them (fig. 18). The whole thickness of the wall of the bowel was heavily infiltrated with leukocytes, many of which were pus cells. They occupied the connective tissue of the

mucosa and extended into the necrotic material on its surface; they were among the fibers of the muscularis mucosae, which at times was hard to identify. They were found in large numbers in the submucosa and in the dilated lymph and blood spaces of it. In some regions, the cellular invasion involved the muscular coats and was found among the fibers of this coat, while at one point in the rectum an exudate of fibrin and pus cells was found outside the visceral peritoneum.

Occasional invasion of a solitary lymph follicle was observed, but this was by no means selective, since the mucosa surrounding each

Fig. 20.—Endameba histolytica entering the submucosa by way of a lymph space in kitten 8; × 350.

invaded follicle was involved in marked degree. The invaded solitary follicles of the colon presented changes comparable with those of the corresponding ileal structure (fig. 19). Here, too, the attack could be traced from the surface to the interior; the destruction was extensive, almost furuncular, with amebas present in great numbers. As in the ileum, there was no invasion of the deeper tissue by extension of the follicular process.

In several places, amebas were found in lymph spaces leading from the mucosa to the submucosa (fig. 20). Rarely such a space, containing

amebas, could be traced in serial sections from the superficial portion of the mucosa to the deeper submucosa. These spaces frequently were filled with leukocytes, as well as with amebas, and often the endothelial lining was injured or destroyed.

In the cecal regions of this animal there were found great spaces outside the mucosa and between the muscle bundles of the circular layer of the bowel (fig. 21). They were sharply defined, were lined in part by a flattened epithelium (endothelium?), and contained finely granular material resembling that found in some of the smaller lymph spaces of the submucosa. Embedded in this granular mass were some leukocytes and pus cells and a few scattered amebas. Exact interpreta-

Fig. 21.—A greatly dilated space (lymph?) in the muscular wall of the cecum of kitten 8; × 75.

tion of this unusual observation is lacking, but I believe it represents a great dilatation of the lymph spaces found normally among the bundles of the muscular coat, that the condition is not strictly amebic in origin, but, rather, that it grew out of those changes initiated by ligation of the bowel. The same changes were not found in any other animal of my series, and no description of similar lesions has come to my attention.

Careful examination of the greatly swollen mesenteric lymph nodes of this animal, in the course of which one node was cut serially and examined throughout, failed to reveal amebas.

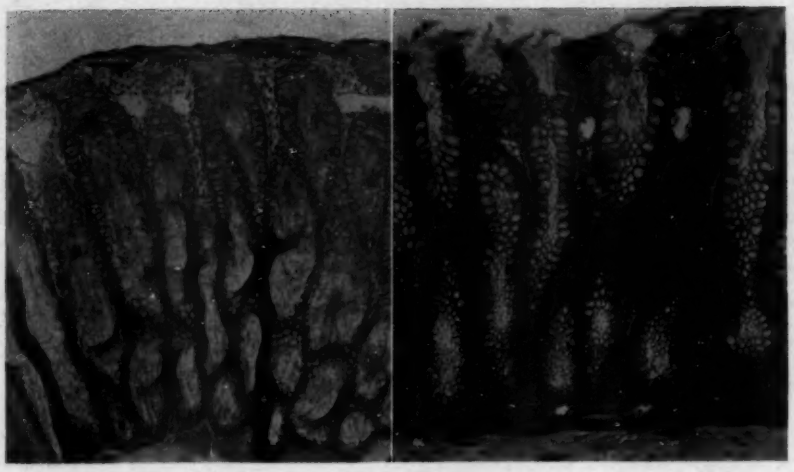
Kitten 7 was given intracecal injections with cultural *Endameba histolytica*, but the lower part of the bowel was ligated and the animal

was otherwise treated as was kitten 8. It was killed three days after inoculation, and at necropsy the pathologic changes were similar to those of the other kitten, except that they were less severe. The colon was not so greatly distended, the ileocecal valve was closed, and the mesenteric lymph nodes were but little, if any, changed. When the bowel was opened, lesions were not evident to the unaided eye, although sections from various regions disclosed superficial amebic destruction of the rectal mucosa in patches. In the regions of amebic attack, as well as in all portions of the colon remote from ulcerative areas, marked vascular congestion appeared, and there was from severe to moderate infiltration of the mucosa and submucosa, with lymphocytes and polymorphonuclear leukocytes. Although less extensive than the lesions presented

Fig. 22.—Endameba histolytica within the necrotic tissue of an intestinal lesion of a kitten showing ingested erythrocytes; × 1000. One ameba with the nucleus in focus contains eight erythrocytes, some partially digested.

in kitten 8, the amebic changes found in this animal varied greatly in nature and extent from those shown in infected kittens without intestinal obstruction.

Kitten 6 had received rectal injection of the ameba-containing stool of a patient, and four times it had been subjected to injection of *Endameba histolytica* from culture; infection had not resulted (strain H, see study 2). This kitten was anesthetized and intracecal injection of the same cultural strain was made, at which time the rectum also was ligated. Four days later, the animal was killed and examined. At the time of necropsy, a small number of sluggishly motile amebas were found in the fluid content of the colon, but neither inspection by the unaided eye nor section and microscopic examination of tissues from various



A B

Fig. 23.—*A*, colonic mucosa of kitten ill with diarrhea but free from amebiasis, showing increased production of mucus; × 75; stained for mucus. Just below the surface are lymph spaces lined by endothelium. *B*, colonic mucosa of same kitten, showing great increase in the number of goblet cells and production of mucus; × 75.

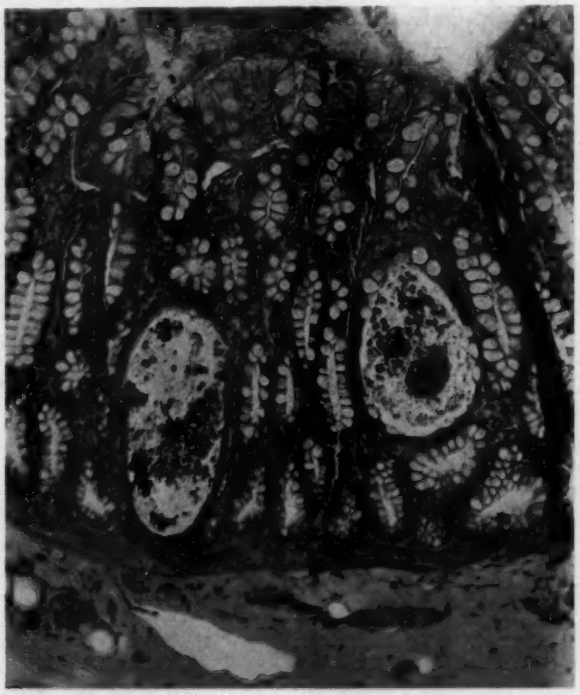


Fig. 24.—Mucosa of colon of kitten ill with diarrhea, but free from amebiasis, showing mucosal crypts containing secreted material, desquamated epithelium and glandular material; × 100.

portions of the bowel revealed amebic lesions. A preparation of the stool that was fixed at the time the necropsy was performed and subsequently stained with iron-hematoxylin showed the amebas present to have the morphologic characteristics of *Endameba histolytica*. It seems more reasonable to suppose that, in this instance, the occluded bowel acted as a living culture tube and that the organisms introduced were able to live and multiply within it, than to believe that those recovered at necropsy were *Endameba histolytica* simply surviving the inoculation as long as four days.

In amebic lesions of the intestines of kittens, the ingestion of erythrocytes by amebas in the deeper portions of the necrotic tissue was commonly observed (figs. 11 *A* and 22). No other recognizable tissue elements were seen within them.

In some of the animals inoculated with *Endameba histolytica* from the stools of man and other kittens, intestinal infections developed that were accompanied by diarrhea, but amebas were not present in the stools and amebic lesions were not present in the bowel. The principal intestinal changes shown by these sick kittens that were free from amebiasis were increased production of mucus (fig. 23 *A*), greatly increased numbers of goblet cells (fig. 23 *B*) and the development of mucosal crypts (fig. 24). These mucus crypts seemed to result from occlusion of mucosal crypts in their superficial portions. This produced, below, a dilated space lined with flattened epithelium and filled with a granular material containing shrunken, desquamated epithelial cells and lymphocytes. Cellular infiltration was usually slight, rarely diffuse and never deeper than the mucosa. No ulcerative intestinal lesions were observed.

COMMENT

Amebic Lesions in Man.—A review of the medical literature dealing with amebiasis, as it appears in man, leads to the opinion that here is an entity of known etiology, presenting distinctive intestinal lesions and, in the main, distinctive complications, both in the tendency to attack certain organs only and in the nature of the pathologic changes produced in them. Disregarding slight differences of opinion concerning the site and nature of the destructive intestinal lesion which results from the action of *Endameba histolytica,* it is agreed that the lesions produced are of a peculiar nature, differing essentially from all other intestinal ulcerations; that they are produced by the cytolytic action of a secretion of the ameba and are accompanied by slight inflammatory reaction; that the lesions, wherever found, present the same destructive changes whether the amebic attack is intestinal, hepatic, pulmonary or cerebral; that the solitary follicles of the intestine, although occasionally involved in the process, are not predisposed to attack; that the changes here vary in no particular from the amebic process elsewhere, unless

it is to show even more widespread destruction than the adjoining intestinal tissue; that the mesenteric lymph nodes are rarely, if ever, invaded by *Endameba histolytica,* unless it is by direct extension of the intestinal process into a node adherent to the bowel as the result of peritoneal irritation, and finally, that the presence of *Endameba histolytica* in the stools means that intestinal lesions are present even in the absence of symptoms of intestinal infection.

Concerning that portion of the bowel first attacked by *Endameba histolytica,* two distinct views have been held: one, that the mucosa is first attacked, and one, that the first or principal change is submucosal. This latter conception was held by the earlier investigators in the field, and probably represents the impressions gained from the study of more advanced lesions in which the mucosa was widely undermined. This might easily lead to the impression that the less extensive mucosal destruction must have arisen secondarily to the more extensive deeper process. Single sections through small, undermined ulcers could disclose a destructive submucosal lesion apparently covered by an intact and nearly normal mucosa. However, a description of a submucosal process covered by mucosa which was not injured by *Endameba histolytica* has not come to my attention.

Among the more recent investigators of amebiasis in man, the belief largely prevails that the intestinal mucosa, rather than the deeper structures, is involved first. Whether the attack is on the superficial epithelium or on the deeper portions of the mucosa, by way of the invaded mucosal crypts, is open to controversy. The lapse of a few minutes in time may determine the presence of the ameba at the bottom of a mucosal crypt. Postmortem destruction of mucosal epithelium is so frequently encountered that it can rarely be interpreted as amebic, even in the presence of the parasite.

It is often difficult in a review of articles in the literature to distinguish between descriptions of lesions that are small and presumably recent and attempts to explain the first tissue changes by the appearances presented at the edges of the advanced lesions. Slight changes in the tissue bordering a deep ulcer are a part of the advanced process and do not necessarily represent the nature of the primary amebic attack.

Amebiasis in the Kitten.—Controversy over the point of primary intestinal attack in amebiasis artificially produced in the kitten has been reduced to that over the portion of the mucosa first involved.

No one has described destruction of the submucosa, except secondarily to lesions of the mucosa. Aside from differences of opinion less vital than those which prevail concerning the exact structures primarily involved in the amebic process, the nature of the intestinal lesion

that results from the action of *Endameba histolytica* in the kitten is believed to be similar to that of man. Here, too, cytolysis, rather than inflammatory destruction, characterizes the lesion. Amebic involvement of the solitary follicles of the colon is incidental only and results, as in man, in an extensive destructive lesion containing amebas in great numbers. In amebic abscess of the liver, the only amebic lesion described as complicating intestinal amebiasis in the kitten, the changes produced are similar to, if not identical with, those in the hepatic lesions of man. Differences presented by amebic lesions in man and the kitten depend, in part, on the tendency for amebiasis in the kitten to remain an acute process with death often resulting before involvement of the submucosa occurs, so that the deeper, undermined intestinal ulcer is less frequently seen. The distribution of intestinal lesions in the kitten, as well as the evidence produced by intestinal occlusion, indicates that stasis is a factor in the production of amebic infection. Slight evidence has been introduced to indicate that *Endameba histolytica* may occupy the intestinal tract of the kitten without producing ulceration.

SUMMARY

Intestinal stasis, minute or gross, is an important factor in making it possible for *Endameba histolytica* to initiate its destructive attack. Examination of very early amebic lesions in the middle portion of the colon revealed that, outside the usual regions of physiologic intestinal stasis, the cecum and the sigmoid, the lesions begin at points of microscopic stasis, i. e., the depths of grooves produced by normal mucosal folds.

In the kitten, *Endameba histolytica* attacks first the most superficial portion of the intestinal mucosa, and destroys the epithelial cells of this region and the mucosal interstitial tissue with equal facility.

In the absence of intestinal obstruction, *Endameba histolytica* does not invade the mucosal glandular crypts until their deeper, expanded portions have become opened by a process of necrosis that has destroyed the superficial half of the mucosa.

In the kitten, tissue is destroyed by the action of a secretion produced by *Endameba histolytica*. Cytolysis at a distance from amebas and out of all proportion to their number is commonly found. Among the conspicuous remote effects of the action of *Endameba histolytica* should be mentioned the absence of mucosal goblet cells at the point of actual necrosis of tissue, as well as in the depths of the glands involved in their superficial portions.

In the kitten, destruction of tissue is not produced by the mechanical action of *Endameba histolytica*. Except that the ameba may invade an occasional mucosal crypt that has been opened by destruction of the

more superficial portion, or except that it may be found in a lymphatic space relatively unchanged, the organism occupies only the necrotic zone resulting from the destruction of tissue.

Solitary lymph follicles are not predisposed to the attack of *Endameba histolytica.* If these follicles are involved, the invasion can be traced into them from the mucosal surface, whereas the lesion produced is an extensive destruction of tissue accompanied by the presence of amebas in large numbers.

A deep amebic intestinal lesion was not observed unaccompanied by superficial destruction of the mucosa above it. The invariable association of the deep lesions with superficial ulceration was occasionally disclosed only by a study of serial sections.

In no case of intestinal amebiasis in the kitten was there invasion of the mesenteric lymph nodes by *Endameba histolytica,* nor did these nodes show cells within them that could easily be confused with *Endameba histolytica.*

In kittens infected by the intracecal injection of cultural *Endameba histolytica* accompanied by the occlusion of the bowel by ligature, the intestinal lesions that developed were so different from those presented by kittens free from intestinal obstructions that conclusions concerning the pathologic changes in amebiasis could not be drawn from them.

Increase in the number of goblet cells, overproduction of mucus and the development of mucosal crypts are nonspecific reactions and were not found more frequently associated with amebiasis than with diarrhea due to other causes.

In the absence of intestinal occlusion, the resistance of the kitten apparently may be so lowered by anesthesia and laparotomy that infection may result from the injection of *Endameba histolytica* grown on starch-containing medium.

Although living *Endameba histolytica* was found at the end of four days in the intestinal content of an occluded colon free from amebic lesions, the highly artificial nature of the experiment, as here conducted, does not warrant the conclusion that *Endameba histolytica* might occupy the intestinal tract of the kitten as a harmless commensal.

Conclusions cannot be drawn concerning the rôle of bacteria in the production or modification of amebic lesions, intestinal or hepatic, in the kitten.

Conclusions concerning culture mediums for the ameba and the results of animal inoculations are given on pages 366 and 385.

CAVERNOUS HEMANGIECTASIA OCCURRING WITHIN A NODULAR GOITER *

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The usual occurrence of pathologic changes, more commonly of the degenerative type, within the blood vessels of nodular goiters is well recognized. Gutknecht [1] observed the formation of hyalin in the vascular walls and even a marked deposition about the capillaries. He also noted other changes, particularly calcification, and pointed out that these involve all the vessels, especially the smallest. Jores [2] found arteriosclerotic changes within the arterial walls independent of a generalized arteriosclerosis. These consisted of intimal thickening and fragmentation of the internal elastic membrane, with the consequent formation of granules and nodules, and calcification. Isenschmid [3] added that in regions where goiter is severely endemic, these arteriosclerotic changes may occur in the thyroid gland early in childhood. He noted, too, that these same changes in the vessels of the thyroid gland are not uncommon after the first year of life. Similar degenerative changes, likewise calcification, occur within the fibrosed and hyaline connective tissue of the stroma. These changes were most common in the nodular goiters occurring in endemic districts, and were much less frequent in the thyroid glands in regions where goiter is more rarely seen. Hesselberg [4] even described arteriosclerotic changes in the superior arteries of the thyroid glands of infants, one a new-born infant. She also figured the dilated blood spaces of the so-called "struma vasculosa" of the new-born infant.

Endemic cretinism may exist with or without goiter. When it exists with goiter, the latter is, as a rule, nodular. Wangensteen [5] described the changes occurring in the blood supply of these cretinous nodular goiters as being associated with an apparent effort to eke out a sufficient amount of thyroid gland secretion from what would seem to be a most barren supply.

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* Submitted for publication, April 25, 1930.

* From the Departments of Surgery and of Pathology of the University of Chicago.

1. Gutknecht: Virchows Arch. f. path. Anat. **99**:419, 1885.
2. Jores: Beitr. z. path. Anat. u. z. allg. Path. **21**:211, 1897.
3. Isenschmid: Frankfurt. Ztschr. f. Path. **5**:205, 1910.
4. Hesselberg: Frankfurt. Ztschr. f. Path. **5**:322, 1910.
5. Wangensteen: Surg. Gynec. Obst. **48**:613, 1929.

Vascular changes, particularly the degenerative types, are thus common in nodular goiters (struma nodosa). While these have been well recognized, described and figured, the particular condition that we are presenting at this time is evidently rare. So far as we have been able to determine, it has been recognized and reported by four previous observers, all pupils of Langhans. Gutknecht, studying a series of sixty goiters removed by Kocher, frequently observed dilatation of the capillaries, particularly those of the goitrous nodules. He noted within the nodules, and especially at their peripheries, that the capillaries became greatly dilated, even becoming cavernous spaces. Von Sinner [6] studied these dilated vessels more extensively and figured one of the areas, which closely resembled a cavernous hemangioma. She also noted the association of the condition with the formation of hematogenous hyalin ("Kautschukhyalin"), as previously described and figured by Wiget.[7] Wegelin [8] has briefly described the entity in his excellent monograph and figured one of these unusual areas of cavernous blood vessels (his fig. 63). Thus far we have been able to find no other references in the literature. Apparently, the condition does not occur in diffuse goiters. If it did, it would seem that it should have been recognized before, particularly in view of the large numbers of thyroid glands that are being removed in this country.

REPORT OF CASE

History.—A housewife, aged 46, entered the University of Chicago Clinics on Nov. 5, 1928, complaining of a recent speech disturbance and weakness in her right arm and leg. After examination, her condition was regarded by Dr. Roy Grinker as due to a transient hemiplegia, probably subsequent to the rupture of a small cerebral vessel. The blood pressure was high, 230 systolic and 130 diastolic, and there had been some edema about the ankles. There was present a large nodular and cystic goiter, involving particularly the right lobe and isthmus.

The patient's mother had a goiter that did not require operation. At the age of 23, the patient first noticed an enlargement of the neck during pregnancy and following the birth of her first child. This increased in size during the second pregnancy and after the birth of her second child. At the age of 26, she had a partial thyroidectomy, in which the left lobe was removed. The enlarged right side and isthmus, however, remained and slowly increased in size. During the past few years, there was increasing dyspnea on exertion, with an occasional mild stridor, and likewise slight dysphagia, particularly when the patient swallowed rather large or irregular masses of food. There was moderate compression of the cervical veins, with some congestion. She noticed cardiac irregularity at times and also that the heart was rapid. However, she was not aware of the symptoms of thyrotoxicosis as ordinarily recognized.

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6. Von Sinner: Virchows Arch. f. path. Anat. **219**:279, 1915.

7. Wiget: Virchows Arch. f. path. Anat. **185**:416, 1906.

8. Wegelin, in Henke-Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 219.

Physical Examination.—Roentgen films of the chest were made, which demonstrated calcification within the wall of a large cyst and an intrathoracic extension of the goiter on the right. The trachea was sharply deviated to the left and compressed by this partially intrathoracic lobe. The cardiac area was estimated as 40 per cent oversize. There was albuminuria. Owing to the recent vascular accident, the patient was not regarded as a good risk, and operation, while considered advisable because of the partial intrathoracic goiter and the pressure symptoms, was postponed for some months. The basal metabolic rate was essentially normal, plus 12, and remained about the same, save for an elevation to plus 18 just previous to operation.

Operation and Subsequent Course.—On March 6, 1929, the right lobe and isthmus were removed under local anesthesia. There was a marked fall in blood pressure, from 220 systolic and 110 diastolic to 132 systolic and 82 diastolic during the luxation of the intrathoracic lobe, which arose from the right side of the isthmus and extended into the superior mediastinum 6 cm. below the clavicle. Convalescence was uncomplicated save for hoarseness, and the patient was dismissed on the sixth day following the thyroidectomy. During the luxation of the partially intrathoracic lobe under local anesthesia, huskiness of the voice developed. This continued after operation, and laryngoscopy on the day following revealed that the right vocal process was fixed in the cadaveric position. Recovery did not ensue, and one year later, in spite of the disappearance of hoarseness, the patient had a paralyzed right vocal cord. The trachea, however, had returned to its normal position and was of normal caliber. The basal metabolism was plus 3 on Oct. 18, 1929, with the pulse rate 80 per minute and the blood pressure 150 systolic and 110 diastolic in the basal state.

Pathologic Observations.—At the time of operation, one of us (P. A. D.) was making a thorough study of our goiter material. In removing large numbers of blocks of tissue for section from the various parts of both excised lobes, and examining them, he discovered the unusual pathologic condition that we report.

The goitrous tissue, removed as two separate lobes of approximately the same size, weighed a total of 410 Gm. The lobes were similar in gross structure, each containing a spherical, firm-walled, cystic mass about 5 cm. in diameter in the superior portion (fig. 1). The walls of the cysts were stiff and fibrous, varying from 1 to 6 mm. in thickness. Each contained calcified granules and plaques. Within the cysts was a firm, elastic, almost rubbery substance, ranging in color from yellow to greenish-brown (fig. 1, *K*). This was slightly adherent to the walls of the cysts. Wiget called this substance "Kautschukcolloid," but stated that it arose from erythrocytes, after hemorrhage. Von Sinner's chemical studies showed that it was essentially hematogenous hyalin and not derived from the glandular colloid, hence it has since been called hematogenous hyalin ("Kautschukhyalin"). The remainder of the goitrous tissue, constituting its greater part, consisted of numerous large and small, firm, colloid nodules, varying in diameter from 2 mm. to 4 cm. Within some of these nodules there was evidence of hemorrhage (fig. 1, *N*), both old and recent. The thyroid gland tissue between the nodules was scanty and largely fibrous.

Microscopic sections from different portions of the two excised lobes revealed that the nodules were colloid, with both large and small follicles. The internodular thyroid gland tissue showed evidence of hyperplasia, with extensive areas in the colloid or resting stage. Groups of thyroid gland alveoli, lined by tall cuboidal to columnar cells, and with scanty or totally deficient colloid content, were in close proximity to extensive groups of larger alveoli with colloid filling their distended lumina. Portions of some sections showed close intermingling of

the two types of alveoli. It is of interest to note that the colloid of many of the larger alveoli displayed a conspicuous vacuolization at its periphery. Fibrosis, edema and hyaline changes were common, and there were numerous hemorrhages into the stroma. There was frequent lymphocytic invasion. Special fixations and special staining procedures showed contrasting mitochondria-rich and mitochondria-poor alveolar cells.

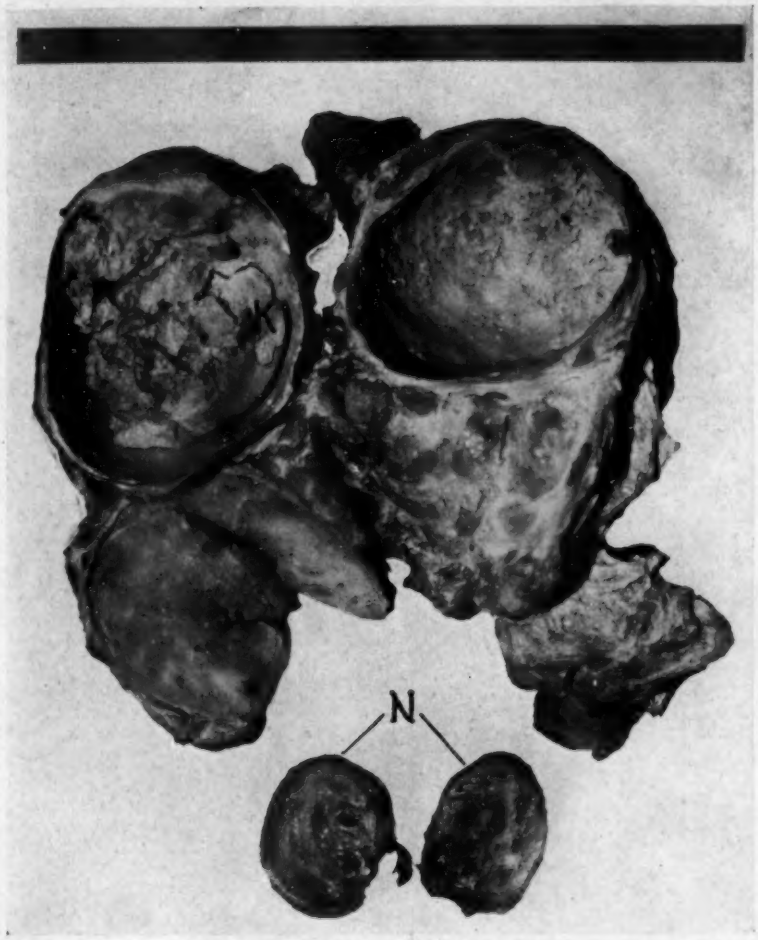

Fig. 1.—The excised isthmic lobe, hemisected to show the cyst (above) with hematogenous hyalin ("Kautschukhyalin"), *K*. The intrathoracic portion, composed of colloid nodules, is below. A sectioned nodule, *N*, reveals fresh hemorrhage.

Although areas of cavernous hemangiectasia (fig. 2) were observed in both lobes, they were far more common in the intrathoracic portion of the isthmic lobe, and it was in this location that the material to be described and figured was found. In the posterior portion of the region representing the thyroid capsule, there was considerable increase in the white, fibrous connective tissue of the stroma. Within

this were several rows of moderately large, round to oval thyroid alveoli, with a generous colloid content, conspicuously vacuolated. The branches of the inferior thyroid arteries in this region showed marked arteriosclerotic changes (fig. 3). Inside this glandular tissue, which was changed by pressure atrophy, was a thick

Fig. 2.—Cavernous dilatation of blood vessels at the margin of a colloid nodule within the intrathoracic portion of a partially intrathoracic nodular goiter.

capsular layer of fairly dense, white, fibrous connective tissue in which were many small capillaries and occasional small groups of thyroid gland alveoli. The inner margin of this fibrous tissue layer gave rise to large trabeculae that separated extensive areas of hemangiectasia. These dilated blood spaces were of widely varying sizes, with thin trabecular walls lined by endothelium. Many of the larger

spaces were divided into smaller blood-containing compartments by thin strands of fine connective tissue lined by endothelium. Some contained distinct capillaries free among the blood cells. Recent organized fibrin thrombi were numerous. These were usually small in comparison with the capillary spaces and were but partially obstructive. The blood in the dilated vascular spaces interestingly displayed erythropoietic tendencies; normoblasts were numerous. Cells of the myelocytic series could not be identified, although mature leukocytes were plentiful.

Fig. 3.—Arteriosclerotic changes within one of the inferior thyroid arteries in the region of the cavernous hemangiectasia.

COMMENT

In considering the nature of this pathologic condition, we have primarily the problem of its origin. Did the cavernous blood spaces originate by proliferative changes of the blood vessels within the goiter, or were they formed by a dilatation of preexisting vessels, associated with some obstruction to the outflow of blood? In short, was it hemangioma or hemangiectasia? There was but little evidence, either in those cases which have been described or in our case, that

there were associated proliferative changes of the vascular walls. On the contrary, the surrounding vessels showed degenerative changes, with obliteration of the lumina and thickening of the walls rather than those neoplastic changes associated with true hemangiomas. There were several factors that indicated that the dilatation was subsequent to an obstruction. First, the cervical veins were large and distended, as the result of pressure of the intrathoracic portion of the goiter. This resulted in venous congestion within the goiter, as noted at the excision. The growing nodule and likewise the obliterative vascular changes themselves possibly resulted in an increase of the venous pressure. The thyroid gland is the most vascular of the larger organs of the body.[9] There was also marked hypertension with the increased vascularity. It is thus understandable how obstruction to the venous outflow might have caused capillary dilatation. Similar conditions, however, occur frequently in goiter, and the condition that we are presenting is apparently rare. Possibly it is more frequent than has been recognized. In the case of hepatic hemangiectases, Moise [10] suggested the persistence of capillaries that normally undergo regressive changes. Both Wiget and von Sinner noted the presence of associated "Kautschukhyalin" degeneration. The presence of hematopoiesis within the cavernous blood spaces argues for a slowing of the circulation as blood coursed through them. This has frequently been recognized in cavernous hemangiomas.[11]

In conclusion, it would appear that the condition is mechanical in its origin and should be regarded as a local hemangiectasia rather than as a neoplastic growth of goitrous blood vessels.

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9. Tschuewsky: Arch. f. d. ges. Physiol. **97**:280, 1903.

10. Moise: Bull. Johns Hopkins Hosp. **31**:369, 1920.

11. Schmieden: Virchows Arch. f. path. Anat. **161**:373, 1900.

Laboratory Methods and Technical Notes

A METHOD OF PRODUCING CHRONIC FOCAL INFECTIONS*

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In experiments bearing on the pathogenicity of bacteria, the usual methods of animal inoculation are entirely at variance with conditions occurring in the human body. The conditions resulting from intravenous or subcutaneous inoculation have little in common with the presence of infected teeth, tonsils or other foci of chronic infection in man. Usually animals so inoculated either succumb or recover promptly; rarely do they manifest the evidences of chronic focal infection.

Several methods have been devised for producing chronic foci of infection in animals. Rosenow and Meisser [1] removed the pulp from root canals in teeth, implanted bacterial inoculation in the canals at the apexes, then closed the canals as in ordinary dental procedures. In dogs so inoculated there developed manifestations of disease similar to the clinical phenomena observed in patients. Dochez and Sherman,[2] in their investigations on scarlatina, produced chronic foci by injecting a mass of soft agar subcutaneously and inoculating it with bacteria. Rhodes and Apfelbach [3] devised the method of implanting surgically small bits of bone impregnated with bacteria into the spleen or elsewhere in dogs. They reported the production of certain phenomena resembling chronic focal infection in human subjects.

A new method, both simple and effective, is the subject of this report. Applicators of cotton, similar to those commonly used for throat swabs, are made on no. 20 or 22 rustless wire rather than on wood. The cotton is wound rather loosely, so that moderate force will slip it off the wire. A trocar and cannula are inserted into the region to be inoculated. The trocar is then withdrawn, leaving the cannula in place. The cotton applicator is dipped into the material to be inoculated and is inserted through the cannula. The swab is pushed beyond the end of the cannula, then, on withdrawing the wire, the end of the cannula pushes off the cotton into the tissue or cavity desired to be infected. The cannula is then withdrawn.

* Submitted for publication, July 11, 1930.

* From the Department of Pathology, Jefferson Medical College.

* This work was made possible by funds from the Martin Research Foundation.

1. Rosenow, E. C., and Meisser, J. G.: The Production of Urinary Calculi by the Devitalization and Infection of Teeth in Dogs with Streptococci from Cases of Nephrolithiasis, Arch. Int. Med. **31**:808, 1923.

2. Dochez, A. R., and Sherman, L.: Tr. A. Am. Physicians **39**:136, 1924.

3. Rhodes, G. B., and Apfelbach, C. W.: J. Infect. Dis. **43**:215, 1928.

The method is merely a simplified procedure for implanting infection in a porous foreign substance within the tissues. The foreign substance serves to maintain the infection against effective body resistance. The method is well suited for producing chronic foci in subcutaneous and intramuscular areas and in the body cavities. By exposing the abdominal viscera the infection may be implanted easily in the spleen, liver, gallbladder or other structures. In such instances, a smaller cannula and correspondingly smaller applicators are used. In small animals a spinal puncture needle of large size makes a suitable cannula. The cotton swab, on fine stiff wire, is wound small enough to pass readily through the lumen of the needle. In some experiments a small intravenous inoculation, consisting of the sediment from 1 or 2 cc. of a twenty-four hour broth culture, was made at the time of the implantation of the infected cotton plug.

Dogs are so resistant to ordinary inoculations that they are seldom used for the purpose. Chronic foci are readily produced in them by this method. When inoculated with streptococci, masses of inflammatory granulations, from 3 to 5 cm. in diameter, develop in a few weeks. On examination weeks or months later the organism inoculated is found in large numbers in the mass about the cotton plug. Occasionally it is found in the blood and in the substance of other organs. *Streptococcus hemolyticus* and *Streptococcus viridans* have been recovered in pure culture regularly after from six to ten months' implantation.

Most of the animals under experimentation have received the inoculation intraperitonally. Contrary to expectations, such inoculation has no tendency to produce generalized peritonitis, except in rare instances when a viscus has been punctured. The peritoneum in animals, as in man, is highly resistant to ordinary methods of infection. The cotton plug is promptly surrounded by folds of the omentum and an immediate local inflammatory reaction results in a growing mass of infected granulation tissue. Such a mass situated in the peritoneal region is a suitable source for the absorption and dissemination of infection or its products to other parts of the body.

The pathologic conditions found in animals inoculated by this method have been varied. A report dealing with rheumatic lesions will follow. The method is described in the hope that it may be of use to those who are interested in chronic infections.

General Review

YELLOW FEVER

A FILTRABLE VIRUS DISEASE *

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With the publication of the conclusive paper of Stokes, Bauer and Hudson [1] in 1928, the era of speculation as to the nature of the etiologic agent in yellow fever, lasting almost half a century, apparently drew to a close. From 1880, when Freire [2] reported a staphylococcus, until 1901, when Durham and Myers [3] described a bacillus, at least six other organisms were held to be the cause of the disease. Undoubtedly, most of these so-called discoveries were greatly influenced by the pure culture method of isolating bacteria described by Koch in 1882. As the disease had been proved to be infectious, and since several diseases by that time had been ascribed to filtrable agents, it does not now seem strange that Reed, Carroll and Agramonte,[4] after the failure of their predecessors to name a correct bacterial agent, should have attempted to filter the causative virus. However, their results, too well known to be described in detail here, seemingly closed the field to further endeavor. Nevertheless, in 1919, Noguchi [5] described his *Leptospira icteroides* (*interrogans*) as the causative agent. His work was accepted, and the organism was named in the textbooks as the cause of yellow fever; but this theory soon met with opposition and now appears to be permanently abandoned since the report of Stokes and his collaborators, which confirmed once more the original work of the American Commission in 1900.

EPIDEMIOLOGY

It is well known that yellow fever is a disease existing in endemic, epidemic and sporadic form. The work of Marchoux and Simond,[6]

* Submitted for publication, July 26, 1930.

* From the Department of Bacteriology, College of Physicians and Surgeons, Columbia University.

1. Stokes, A.; Bauer, J. H., and Hudson, N. P.: Am. J. Trop. Med. **8**:103, 1928.
2. Freire, D., cited by Agramonte, A.: Ann. Int. Med. **2**:138, 1928.
3. Durham, H. E., and Myers, W.: Brit. M. J. **1**:450, 1901.
4. Yellow Fever, a Compilation of Various Publications, Document 822, Sixty-First Congress, Third Session, 1912.
5. Noguchi, H.: J. Exper. Med. **29**:565, 1919.
6. Marchoux, E., and Simond, P. L.: Ann. de l'Inst. Pasteur **20**:104, 1906.

published in 1906, which has been amply confirmed, showed that the disease was endemic in those countries where adult *Aedes aegypti* could live the whole year through, that it was epidemic in those countries where the mosquitos could survive part of the year, and that it was sporadic in those places where a focus of infection was set up by immigrants infected aboard ship or in some foreign country. They also demonstrated that the virus was propagated in endemic areas by benign cases in children, and in epidemic areas by infected mosquitos accidentally admitted to the country. The same authors stated that no race appeared to possess natural immunity, nor did any age group, and that the disease was benign in children and severe in adults. Hanson,[7] in a statistical report on an epidemic in 1921, found the lowest death rate between the ages of 5 and 15; however, the highest rate was in children between the ages of 1 and 3, and the incidence of infection seemed to be slightly higher in males than in females.

INSECT VECTORS

One of the principal observations made by Stokes, Bauer and Hudson,[1] and since confirmed by Mathis, Sellards and Laigret,[8] Aragao[9] and Hindle,[10] was that yellow fever is transmissible from man to monkey and from monkey to monkey by the bite of *A. aegypti*. *A. aegypti* is the mosquito which was found able to transmit the experimental disease from man to man by both the American and French Commissions and has accordingly been accepted as the insect vector of the disease. An excellent review on the historical aspects of the relation of insect vectors to yellow fever has been recently written by Agramonte.[2] With the rebirth of investigation in 1927, it is not surprising that new possible vectors were found. Accordingly, Bauer[11] in 1928 named three new species that he found capable of transmitting the infection from rhesus to rhesus. They were *A. luteocephalus, A. stokesi* and *Eretmopodites chrysogaster*. The experimental infection was caused by biting in each case, and also by injection of a macerated suspension of the last named insect. Since then eleven new species able to transmit the infection have been described. *A. vittatus, A. africanus* and *A. simpsoni* transferred the infection, both by biting and by injection, according to Philip.[12] *A. scapularis, A. serratus* and

7. Hanson, H.: Am. J. Trop. Med. **9**:233, 1929.

8. Mathis, C.; Sellards, A. W., and Laigret, J.: Compt. rend. Acad. d. sc. **186**:604, 1928.

9. Aragao, H. de B.: Mem. do Inst. Oswaldo Cruz, 1928, no. 2 (supp.), p. 35.

10. Hindle, E.: Brit. M. J. **1**:976, 1928.

11. Bauer, J. H.: Am. J. Trop. Med. **8**:261, 1928.

12. Philip, C. B.: Am. J. Trop. Med. **9**:267, 1929.

A. taeniorhynchus, reported by Davis and Shannon,[13] have been infectious by injection in all instances and also in the case of the first by biting. *A. irritans, A. nigricephalus, A. punctocostalis, Culex thalassius* and *Taeniorhynchus africanus* have been able by injection, in all cases, to transmit the infection, as recently announced by Philip.[14] The last named could also infect by its bite.

On the other hand, the following mosquitos have not been able to produce the disease either by biting or by injection: *A. apecoargentus, A. longipalpis, A. welmani* and *C. nebulosus,* according to Bauer;[11] *A. hastatus,* as reported by Davis and Shannon;[13] and *Anopheles gambiae,* according to Philip.[14b] Davis and Shannon[13] also announced doubtful results with *C. quinquefasciatus.* It is interesting to recall that in 1906 Marchoux and Simond[6] obtained negative results in man with *A. taeniorhynchus* and also with *A. scapularis, Psorophora ciliata, P. ciliata* and *P. posticata.* The significance of the successful work reported by the investigators named in the preceding paragraph is made clear by the recent observation of Hudson and Philip,[15] who showed that rhesus monkeys experimentally infected could transmit the disease to mosquitos two days before the onset of symptoms. By analogy it may be that human beings, before they themselves have become sick, can and have transmitted the infection to some of these tree-breeding mosquitos hitherto not considered as actual insect vectors.

It is generally assumed that the female mosquito is the intermediate host, and so most, if not all, of the experimentalists have used that sex for their work. However, Aragao[16] recently made two interesting and perhaps significant contributions, namely, that the males of *A. aegypti* are capable of transferring the experimental disease and that if infected females are kept with uninfected males, the latter acquire the ability to infect monkeys. On the other hand, if infected males are harbored in the same container as uninfected females, the latter too become infected. The significance of the last observation is evident: the disease can be transmitted from insect to insect without the necessity of the intervention of a human host, as has hitherto been believed necessary. Theoretically, then, it is possible for the virus of yellow fever to be present in a given vicinity without any clinical or subclinical cases existing. The possibility of an outbreak of yellow fever in India is a conclusion that might be drawn from the recent work of Dinger,

13. Davis, N. C., and Shannon, R. C.: J. Exper. Med. **50**:803, 1929.

14. Philip, C. B.: (*a*) Am. J. Trop. Med. **10**:1, 1930; (*b*) Science **71**:614, 1930.

15. Hudson, N. P., and Philip, C. B.: J. Exper. Med. **50**:583, 1929.

16. Aragao, H. de B.: Mem. do Inst. Oswaldo Cruz, 1929, no. 9 (supp.), p. 193.

Schuffner, Snidjers and Swellengrebel,[17] who have found that an Indian species of *A. aegypti* is capable of transmitting the disease to monkeys of the species *Macacus rhesus*. As the species is indigenous to that country, the stage is set for a possible epidemic. More recently Pettit, Roubaud and Stefanopoulo,[18] working with species of the same insect from Java, Tunis and Cuba, reported similar success, and previously Hindle,[19] working with an Indian strain, was able to do the same, but in neither investigation were the positive results regularly obtained.

It has been known since the beginning of the century [20] that mosquitos cannot infect human beings by biting until the twelfth day after an infectious meal. This observation has been corroborated by Stokes, Bauer and Hudson,[1] and by Bauer and Hudson,[21] who found, in their experimental work on monkeys, that the extrinsic period was from eight to sixteen days or slightly longer. No developmental cycle of the virus, with a possible noninfectious stage in the mosquito, has been mentioned in the literature. Moreover, it has been shown by Bauer and Hudson,[21] Aragao,[9] Aragao and da Costa Lima [22] and Davis and Shannon [23] that macerated mosquitos, during the entire so-called extrinsic incubation period, and different body parts, such as the head, thorax and abdomen and even the dejecta, for part of the incubation period, are infectious for monkeys by injection. However, the question as to why the saliva is noninfectious for at least eight days has not been answered. Perhaps, according to some preliminary work by Aragao and da Costa Lima, the answer lies in the fact that this secretion is actually infectious at an earlier time than has been believed. In a previous report [22b] they had shown that a watery suspension of the feces of an infected insect placed in the conjunctival sac or on the unabraded skin in the inguinal region can sometimes produce yellow fever in the rhesus. Accordingly, in an experiment to determine the minimum incubation period in mosquitos,[24] in which the possible error of fecal contamination was obviated, they were able to show that this period

17. Dinger, J. E.; Schuffner, W. A. P.; Snidjers, E. P., and Swellengrebel, N. H., cited by Pettit, Roubaud and Stefanopoulo, footnote 18.

18. Pettit, A.; Roubaud, E., and Stefanopoulo, G.: Compt. rend. Soc. de biol. **104**:60, 1930.

19. Hindle, E.: Tr. Roy. Soc. Trop. Med. & Hyg. **22**:405, 1929.

20. Footnote 4. Marchoux, E.; Salimbeni, A., and Simond, P. L.: Ann. de l'Inst. Pasteur **17**:665, 1903.

21. Bauer, J. H., and Hudson, N. P.: J. Exper. Med. **48**:147, 1928.

22. Aragao, H. de B., and da Costa Lima, A.: Mem. do Inst. Oswaldo Cruz, 1929, (*a*) no. 8 (supp.), p. 105; (*b*) no. 9 (supp.), p. 136; (*c*) no. 9 (supp.), p. 142, and (*d*) no. 10 (supp.), p. 253.

23. Davis, N. C., and Shannon, R. C.: Am. J. Hyg. **11**:335, 1930.

24. Aragao, H. de B., and da Costa Lima, A.: Mem. do Inst. Oswaldo Cruz **23**:102, 1930.

could be as low as four days. However, they have not, in one attempt, repeated their result and final decision must be held in abeyance.

A question which has arisen in the minds of present investigators is: How long does a mosquito remain infectious after a blood virus meal? The answer appears to be that infectivity is lifelong; as demonstrated by Stokes, Bauer and Hudson,[1] Hindle,[19] Aragao and da Costa Lima [22] and Davis and Shannon,[23] the whole insect or various parts thereof, such as the head, thorax, salivary gland, hemocelic fluid, abdomen, ovaries, midgut and hindgut, are infectious for the periods of time studied. The maximum survival time of the virus reported for any single experiment was 113 days, reported by the first named authors. Incidentally, no statement has been found in the published works that the virus is harmful for the mosquito and so brings about its demise. A second question asked is: Do adults transmit the infection to their progeny? The answer is in the negative. Marchoux and Simond [6] reported successful transfer of infection from the adult mosquito to the first generation. However, Rosenau and Goldberger [25] and more recently Stokes, Bauer and Hudson,[1] Philip [26] and Davis and Shannon [23] obtained negative results.

YELLOW FEVER CONTROL

In 1911, Boyce [27] said that if in areas in which yellow fever was present piped water supplies were installed the disease would soon disappear. This statement is still held to be true, as evidenced by the methods of control employed. At the beginning of the century, such methods as the destruction of larvae in endemic areas, the screening of domiciles, the destruction of mosquitos in the homes of the sick, the prevention of breeding by mosquitos on shipboard and the quarantine of immigrants from endemic and epidemic areas were resorted to.[20] In the last decade, emphasis has shifted to other measures. In areas of endemic and epidemic disease, according to Connor [28] and Hanson,[29] the primary steps taken are the hermetic sealing of water receptacles wherever possible and the placing of bottom-feeding fishes in cisterns, wells and water barrels and top-feeding fishes in fountains. In addition, in epidemic areas, as reported by Carter [30] and Dunn and Hanson,[31] the mosquito-breeding areas are destroyed in ports, centers of travel and large towns.

25. Rosenau, M. J., and Goldberger, J.: Bull. Yellow Fever Inst., 1906, no. 15.
26. Philip, C. B.: J. Exper. Med. **50**:703, 1929.
27. Boyce, R. W.: Yellow Fever and Its Prevention, New York, E. P. Dutton & Company, 1911.
28. Connor, M. E.: Am. J. Trop. Med. **2**:487, 1922; **3**:105, 1923.
29. Hanson, H.: Am. J. Trop. Med. **5**:393, 1925.
30. Carter, H. R.: Am. J. Trop. Med. **2**:87, 1922.
31. Dunn, L. H., and Hanson, H.: Am. J. Trop. Med. **5**:401, 1925.

THE NATURAL INFECTION IN MAN

The clinical manifestations of yellow fever have been too well described in the past to need repetition here.[32] However, in the last few years some new diagnostic aids have been reported. Davis and Burke [33] stated that doubtful cases can be diagnosed by injecting into a monkey blood taken during the early febrile period and then observing the result of the inoculation. Aragao [9] also mentioned a method of postdiagnosing doubtful cases: If some convalescent serum is injected into a monkey and followed in twenty-four hours by a certainly fatal dose of virus, the animal should survive if the disease is yellow fever.

In the past few years, clinical studies of the urine were reported by Penido,[34] of the cerebrospinal fluid, by Lacorte and Villela;[35] of the coagulability of the plasma, by Vellard and Vianna;[36] of the serum alexin, by da Costa Cruz,[37] and of the heart, by Chagas and de Freitas.[38]

Instances of cerebral complications were pointed out by Hanson [39] and more recently by Theiler.[40] Similar symptoms have appeared in numerous filtrable virus diseases,[41] but the cause of this manifestation is a matter of dispute.

In 1890, Councilman [42] described the morbid anatomy of the liver and kidney. Since then the pathologic changes have also been well described by Otto and Neumann,[32] da Rocha Lima,[43] Elliott [32] and others. More recently Hoffmann,[44] Klotz and Simpson,[45] Hudson [46] and

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32. Footnote 4. Boyce (footnote 27). Otto, M., and Neumann, R. O.: Ztschr. f. Hyg. u. Infektionskrankh. **51**:357, 1905. Thomas, A. W.: Ann. Trop. Med. **4**:119, 1910. Seidelin, H.: Bull. Yellow Fever Inst., 1911, no. 1, p. 55. Elliott, C. A.: Arch. Int. Med. **25**:174, 1920.

33. Davis, N. C., and Burke, A. W.: J. Exper. Med. **49**:975, 1929.

34. Penido, J. C. N.: Mem. do Inst. Oswaldo Cruz, 1928, no. 2 (supp.), p. 69.

35. Lacorte, J. G., and Villela, G. G.: Mem. do Inst. Oswaldo Cruz, 1928, no. 2 (supp.), p. 63.

36. Vellard, J., and Vianna, M.: Mem. do Inst. Oswaldo Cruz, 1929, no. 7 (supp.), p. 86; Compt. rend. Soc. de biol. **101**:952, 1929.

37. Da Costa Cruz, J.: Compt. rend. Soc. de biol. **101**:948, 1929; Mem. do Inst. Oswaldo Cruz **23**:131, 1930.

38. Chagas, E., and de Freitas, L.: Mem. do Inst. Oswaldo Cruz, 1929, no. 7 (supp.), p. 79.

39. Hanson, H.: Am. J. Trop. Med. **6**:261, 1926.

40. Theiler, M.: Science **71**:367, 1930.

41. McIntosh, J.: Brit. M. J. **2**:334, 1928.

42. Councilman, W. T.: Pub. Health Bull., 1890, no. 2, p. 151.

43. Da Rocha Lima, H.: Verhandl. d. deutsch. path. Gesellsch. **15**:163, 1912.

44. Hoffmann, W. H.: J. Trop. Med. **27**:235, 1924.

45. Klotz, O., and Simpson, W.: Am. J. Trop. Med. **7**:271, 1927; Am. J. Path. **3**:483, 1927.

46. Hudson, N. P.: Am. J. Path. **4**:419, 1928.

Cannell [47] redescribed the changes in various organs. Intranuclear inclusions described a short time since will be considered in the discussion of the experimental disease.

THE EXPERIMENTAL DISEASE IN ANIMALS

Stokes, Bauer and Hudson,[1] in 1928, first reported the successful transmission of yellow fever from man to *Macacus rhesus*. Their work has been amply verified by Aragao,[9] da Cunha and Muniz,[48] Mathis, Sellards and Laigret,[8] Sellards and Hindle,[49] Pettit, Stefanopoulo and Aguessy [50] and Kuczynski and Hohenadel,[51] and the rhesus has become the animal of choice in yellow fever research. An interesting fact in this connection is that most, if not all, of the successful transfers of the infection from man to monkeys have been with the blood from relatively benign cases, whereas attempts to transmit the disease with material from severe cases have generally resulted in failure.[52]

Other monkeys have been found susceptible to yellow fever by several routes of infection with various infectious materials. A tabulation of monkeys that have been found to be sensitive is as follows: *Macacus sinicus,* by Stokes, Bauer and Hudson,[1] whose results were confirmed by Pettit, Stefanopoulo and Kolochine; [53] *M. cynomolgus* and *M. speciosus,* by Aragao,[9] the susceptibility of the first named being confirmed by da Cunha and Muniz [48] and by Pettit and Stefanopoulo; [54] *Cebus macrocephalus,* by Davis and Shannon; [55] *Ateles ater, Saimiri sciurea* and possibly *Lagothrix lagotrica,* by Davis,[56] and *M. innuus,* by Pettit and Stefanopoulo.[57] In 1907, Thomas [58] obtained apparently positive results with the chimpanzee, but Stokes, Bauer and Hudson,[1] working with the same animal, had doubtful success. Mosquitos and monkey tissues containing the virus have been employed to infect

47. Cannell, D. E.: Am. J. Path. **4**:431, 1928.

48. Da Cunha, A. M., and Muniz, J.: Mem. do Inst. Oswaldo Cruz, 1928, no. 2 (supp.), p. 51.

49. Sellards, A. W., and Hindle, E.: Brit. M. J. **1**:713, 1928.

50. Pettit, A.; Stefanopoulo, G., and Aguessy, C.: Compt. rend. Soc. de biol. **99**:258, 1928.

51. Kuczynski, M. H., and Hohenadel, B.: Klin. Wchnschr. **8**:9 and 58, 1929; Lancet **1**:180, 1930.

52. Stokes, Bauer and Hudson (footnote 1). Mathis, Sellards and Laigret (footnote 8). Aragao (footnote 9).

53. Pettit, A.; Stefanopoulo, G., and Kolochine, C.: Bull. Acad. de méd., Paris **102**:98, 1929.

54. Pettit, A., and Stefanopoulo, G.: Compt. rend. Soc. de biol. **102**:561, 1929.

55. Davis, N. C., and Shannon, R. C.: J. Exper. Med. **50**:81, 1929. Davis, N. C.: Am. J. Hyg. **11**:321, 1930.

56. Davis, N. C.: J. Exper. Med. **50**:703, 1930.

57. Pettit, A., and Stefanopoulo, G.: Compt. rend. Soc. de biol. **104**:63, 1930.

58. Thomas, A. W.: Brit. M. J. **1**:138, 1907.

monkeys. Infected insects were allowed to bite the monkeys or their macerated and emulsified bodies were injected into the animals.[59] The subcutaneous, intraperitoneal, intrahepatic and percutaneous routes have been used for infection with monkey blood or serum taken during the first days of fever, when virus is found in those tissues, or with organs such as the liver, kidney, spleen and brain of animals dead of yellow fever.[60] That very small amounts of virus can produce infection has been definitely established.[61] The bite of a single mosquito or the injection of 1 cc. of a 1 : 1,000,000 saline suspension of macerated mosquito or monkey blood virus has proven fatal.

In contrast with the relative ease with which monkeys can be infected by organs of animals dead of the disease, it has not as yet been found possible to infect these animals with organs of human beings dead of yellow fever,[62] all successful transfers from man to monkey having been obtained by means of blood virus. No explanation for this phenomenon has been advanced.

The disease in monkeys is similar to that in man, and the incubation period is generally from one to fifteen days, although it is sometimes slightly longer.[63] The terminal stage of fatal cases is marked by extreme prostration and subnormal temperature, most animals dying in from four to ten days.[1] Some authors have considered 104 F. as a significant temperature, although it has been shown that animals often have died of yellow fever without ever having a febrile reaction.[64] Recently Pettit and Stefanopoulo [65] corroborated this observation.

The pathology is similar to that of man,[66] and as in the human disease, nuclear inclusion bodies are found.

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59. Stokes, Bauer and Hudson (footnote 1). Mathis, Sellards and Laigret (footnote 8). Aragao (footnote 9). Da Cunha and Muniz (footnote 48). Sellards and Hindle (footnote 49).

60. Stokes, Bauer and Hudson (footnote 1). Aragao (footnote 9). Hindle (footnote 19). Da Cunha and Muniz (footnote 48). Pettit, Stefanopoulo and Aguessy (footnote 50). Davis and Shannon (footnote 55). Davis (footnote 55). Bauer, J. H., and Hudson, N. P.: Am. J. Trop. Med. **8**:371, 1928. Cowdry, E. F., and Kitchen, S. F.: Science **69**:252, 1929; Am. J. Hyg. **11**:227, 1930. Theiler, M., and Sellards, A. W.: Ann. Trop. Med. **22**:449, 1928.

61. Bauer (footnote 11). Philip (footnote 12). Aragao and da Costa Lima (footnote 24). Lewis, P. A.: J. Exper. Med. **52**:113, 1930.

62. Aragao (footnote 9). Pettit, Stefanopoulo and Kolochine (footnote 53).

63. Stokes, Bauer and Hudson (footnote 1). Aragao (footnote 9). Hindle (footnote 19). Davis, N. C., and Shannon, R. C.: J. Exper. Med. **50**:793, 1929.

64. Stokes, Bauer and Hudson (footnote 1). Da Cunha and Muniz (footnote 48). Theiler and Sellards (footnote 60).

65. Pettit, A., and Stefanopoulo, G.: Compt. rend. Soc. de biol. **102**:719, 1930.

66. Stokes, Bauer and Hudson (footnote 1). Hudson (footnote 46); Am. J. Path. **4**:395 and 407, 1928.

A number of primates and lower animals have been found to be refractory to yellow fever. Rabbits, white mice, white rats, puppies, kittens, goats and several species of African monkeys are insusceptible, according to Stokes, Bauer and Hudson.[1] *Pseudocebus azarae,* as reported by Aragao,[9] and *Papio sphinx, Cercopithecus callitrichus, Cynocephalus hamadryas* and *Cercopithecus griseoviridis,* as stated by Pettit and Stefanopoulo,[67] resist infection.

However, Theiler [40] a short time since reported successful transfer of the virus to white mice. He claimed that by the intracerebral, intraspinal and intra-ocular routes, he had passed the virus through this species at least forty-two times and had secured a fixed virus. He was not as successful, however, with the intraperitoneal and subcutaneous routes. At death, virus was recovered from the brain, spinal cord, peripheral nerves and adrenal glands. There were few macroscopic changes in the dead mice, except for hemorrhage into the stomach, which occurred in about 50 per cent of the cases. The significance of this adaptation of the virus to the brain is not as yet clear, although it is a well known fact that some filtrable viruses can be readily adapted to that organ. Herpes simplex, vaccinia, rabies and, as shown more recently, psittacosis [68] are capable of producing death in some primates or lower animals following intracerebral inoculation.

Kuczynski and Hohenadel [51] recently reported successful transfer of the infection to guinea-pigs, although da Cunha and Muniz [48] and Mathis, Cazanove and Bacque,[69] among others, previously reported negative results with the same animal.

INTRANUCLEAR INCLUSIONS

Torres,[70] in 1928, first described inclusion bodies in the nuclei of the liver cells of diseased monkeys. However, Stokes, Bauer and Hudson,[1] in referring to the pathology of *rhesus* liver cells, said that "in some specimens the nuclei of altered cells contained small acidophilic granules," and in 1890 Councilman [42] in a pathologic description of the liver apparently also saw these bodies. Torres' work on the *rhesus* was verified by Cowdry and Kitchen [60] and by Penna and de Figuerrido.[71] The former found nuclear inclusions in the adrenal glands and showed

67. Pettit and Stefanopoulo (footnote 54). Pettit, A.; Stefanopoulo, G., and Kolochine, C.: Compt. rend. Soc. de biol. **99**:260, 1928.

68. Rivers, T. M., and Berry, G. P.: Proc. Soc. Exper. Biol. & Med. **27**:802, 1930.

69. Mathis, C.; Cazanove, F., and Bacque, M.: Bull. Soc. path. exot. **20**:1025, 1927.

70. Torres, C. M.: Mem. do Inst. Oswaldo Cruz, 1928 (supp.) no. 2, p. 55; Compt. rend. Soc. de biol. **99**:1344, 1655, 1660, 1669 and 1671, 1928; **101**:951, 1929; **102**:410 and 414, 1929.

71. Penna, O., and de Figuerrido, B.: Compt. rend. Soc. de biol. **103**:1346, 1930.

also that the inclusions exist in human liver cells. The latter observation was confirmed by Torres [70] and by Hoffmann.[72] Recently Theiler,[40] in his work on the mouse, said that in the brain "the ganglion cells undergo necrosis and there are invariably present eosinophilic nuclear changes resembling those present in the liver of man and monkey dead of yellow fever, and described as inclusions by Torres and Cowdry."

The inclusions are diagnostic for the experimental disease in monkeys, being almost constantly present, although Cowdry and Kitchen [60] found them in only ten of thirty-seven specimens of human liver. Torres [70] also reported the inclusions as being rare in the human disease.

In the experimental infection, the acidophil changes are found in animals killed on the first day of the febrile reaction and continue to increase until the period of hypothermy is reached. In recovered animals, no trace of the inclusions are found, and the organs usually have a normal appearance,[73] a fact that may explain why recovery from the disease usually has no sequelae. Torres [70] reported that his inclusions corresponded to those described for herpes zoster, symptomatic herpes, varicella and virus III, and Cowdry and Kitchen [60] stated that their inclusions were of the same general type as those of herpes, chickenpox, submaxillary disease and virus III, but different in detail. Intranuclear inclusions were not found in mosquitos (Cowdry and Kitchen [60]), which might be an explanation for the fact that the virus has no effect on the insect.

IMMUNITY

Active Immunity.—It has been known for a long time that human beings who have recovered from benign or severe attacks of yellow fever seldom suffer recurrences, and that immunity lasts a long time, if not for life.[74] Experimental confirmation of this fact was presented recently in the work of Bauer and Hudson and their collaborators [75] and that of Sawyer, Kitchen, Frobisher and Lloyd.[76] The technic of this work is as follows: A small quantity of serum from a human being who has recovered from the disease is injected into a *rhesus* monkey a short time before the animal is infected with a fatal dose of virus. If the monkey survives the injection of the virus or has only a very mild

72. Hoffmann, W. H.: Arch. f. Schiffs- u. Tropen-Hyg. **33**:411, 1929.

73. Cowdry and Kitchen (footnote 60). Torres (footnote 70).

74. Marchoux and Simond (footnote 6). Carter, H. R.: Ann. Trop. Med. **10**: 153, 1916.

75. Hudson, N. P.; Bauer, J. H., and Philip, C. B.: Am. J. Trop. Med. **9**:1, 1929. Hudson, N. P.; Philip, C. B., and Davis, G. E.: Am. J. Trop. Med. **9**: 223, 1929. Bauer, J. H., and Hudson, N. P.: J. Prev. Med. **4**:177, 1930.

76. Sawyer, W. A.; Kitchen, S. F., Frobisher, M., Jr., and Lloyd, W.: J. Exper. Med. **51**:493, 1930.

illness, the serum is regarded as having protective properties. By the use of this method it has been shown that serums taken from human beings as late as twenty-three or even twenty-six years after recovery from the disease can protect monkeys.[77]

It is not surprising in view of these facts that monkeys which have recovered from the experimental disease are immune to further infection. This has been shown by Davis,[78] Hindle,[19] Sawyer and his collaborators [76] and others.

The French Commission (Marchoux, Salimbeni and Simond [20]) in 1903 showed that human virus-containing serum heated at 55 C. for five minutes and virus-containing blood kept under a petrolatum seal for eight days protected human beings against the disease. Recently Frobisher [79] showed that monkey virus-containing serum heated at 60 C. for twenty minutes and injected in large quantities protected animals of the same species, although no passive protective properties were demonstrated in the serums of these monkeys. Using the same animals, Hindle [19] and Pettit, Stefanopoulo and Kolochine [53] corroborated the observation on the protective properties of virus attenuated by storage. Hindle also protected monkeys by the injection of diluted virus and prepared vaccines of formaldehydized or phenol-glycerinated livers and spleens of monkeys dead of the disease, which protected the animals when they were tested for immunity as late as six months after vaccination. Aragao [9] used this vaccine in Brazil on 300 people with no untoward results, and Hindle himself stated that he intended to submit his vaccine to a practical field test.

Passive Immunity.—It has been shown that serum of artificially immunized animals, as well as that of recovered human beings, as mentioned, exhibits protective properties. In 1928, Pettit, Stefanopoulo and Frasey [80] prepared antiserums by the injection of monkey virus-containing livers into such naturally refractory animals as the horse and monkeys of the genus *Cynocephalus* and of the genus *Cercopithecus*. If some of this serum was mixed with a fatal dose of virus and thirty minutes later injected into susceptible monkeys, or if the virus and serum were injected separately, the monkeys were protected. Later, the same authors prevented the death of monkeys by the use of the serums as late as five days after the experimental infection.

Antibodies.—That neutralizing antibodies are present in immunized animals was pointed out in the work mentioned in the preceding para-

77. Bauer and Hudson (footnote 75). Sawyer; Kitchen; Frobisher Lloyd (footnote 76).

78. Davis, N. C.: J. Exper. Med. **49**:985, 1929.

79. Frobisher, M., Jr.: Am. J. Hyg. **11**:300, 1930.

80. Pettit, A.; Stefanopoulo, G., and Frasey, V.: Compt. rend. Soc. de biol. **99**:541 and 1114, 1928.

graph, and a short time ago Theiler [40] confirmed this observation when he noted that both human and monkey immune serum could neutralize mouse virus-containing brain. It is almost unnecessary to reiterate that protective antibodies are present in the serums of recovered human beings.

There is some controversy as to the presence of alexin-fixing antibodies. In 1928, Aragao [81] reported negative results, using as antibody human convalescent serums taken from eight to fifteen days after recovery, and as antigens either human serums taken on the first and second days of illness or phenolated saline emulsion of monkey yellow fever liver. However, in 1929, Frobisher [82] claimed successful results in 78 per cent of his attempts to demonstrate the same antibodies. He used both human and monkey convalescent and immune serums as antibody, and as antigen a saline suspension of monkey yellow fever liver and spleen. Nevertheless, he reported unsuccessful results with the precipitin and nonspecific agglutination tests.[79] As antigens for his precipitin tests he used urine of monkeys which had succumbed to the disease, aqueous extracts of monkey liver and alcoholic extracts of the liver and heart. For the nonspecific tests, he used as antigen various members of the *proteus* group of organisms, members of the colon-typhoid group and various species of micrococci. The antibody used in both tests was the same as in the complement-fixation tests.

As regards the presence of any local immunity, Hindle [19] reported that the liver and the spleen of recovered animals protected other monkeys against infection, whereas the brain and the kidney did not. This author stated it as his belief that protection was not secured by the residual virus remaining in these tissues, but that the phenomenon is an example of special tissue immunity. However, the spleen and the liver are two organs that do harbor virus during the disease, and it has been shown that fowlpox virus is recoverable from fowls immune to that disease, and more recently, that vaccine virus is recoverable from animals immune to that virus.[83] Certainly there is no local skin immunity, as shown by Frobisher,[79] who reported negative results using yellow fever serums, virus-containing tissue extract and fresh virus-containing blood in sick, recovered and normal monkeys.

The possibility of a state of hypersensitiveness to yellow fever virus was also pointed out by Hindle.[19] He cited the case of four monkeys that had had mild infections and had recovered and had then been hyperimmunized without any untoward reaction. On retesting these animals with the virus over a period of from two to seven months after

81. Aragao, H. de B.: Compt. rend. Soc. de biol. **99**:1341, 1928.

82. Frobisher, M., Jr.: Proc. Soc. Exper. Biol. & Med. **26**:846, 1929.

83. Sanfelice, F.: Ztschr. f. Hyg. u. Infektionskrankh. **107**:357, 1927. Olitsky, P. K., and Long, P. H.: J. Exper. Med **50**:263, 1929

the last injection, they all died with some symptoms of yellow fever. However, the course of illness ran only for two days, a much shorter period than in normal animals experimentally infected, and no virus was recovered from their organs. In contrast with these monkeys, two others that had also been hyperimmunized did not react when tested at the same intervals.

THE VIRUS

As the strains of yellow fever virus now in use have been isolated both in Africa and in South America, it has been of interest to ascertain whether or not they are identical, so far as the means for determining their unity permits. That there is no discernible difference has been readily proved. This was shown by cross-immunity tests in monkeys, with strains from both continents, by Aragao [9] and by Sawyer, Kitchen, Frobisher and Lloyd; [76] and by cross-protection tests with convalescent serums by Hudson, Bauer, Philip and Davis,[75] by Sawyer, Kitchen and Frobisher,[76] by Davis [78] and by Theiler and Sellards.[84] Klotz and Simpson [45] and Hoffmann [85] showed by anatomic comparison that the lesions of the liver were identical in human beings dead of the disease in Africa and in the Western Hemisphere. Cowdry and Kitchen [60] showed that the inclusion bodies were also identical.

Blanc, Caminopetros and Giroud [86] could not protect human beings against experimental dengue fever by injections of yellow fever serums prepared in rabbits or obtained from human convalescents, thus showing that these two viruses are not related.

Since it has become apparent that the causative agent belongs to the ultramicroscopic group, the effects of various chemical and physical agents on it have been determined in an attempt to classify it with the other filtrable viruses. Frobisher [79] showed that mercuric chloride 1:7,500, hexylresorcinol 1:1,500, phenol 1:150 and sodium oleate 1:150 did not inactivate the virus after contact at 30 C. for thirty minutes. He also asserted that under the same conditions the virus was inactivated, but not necessarily killed, by the following: eosin 1:300, liquor cresolis compositus (U. S. P.) 1:200, sodium oleate 1:50, formaldehyde 1:15 and ethyl alcohol 1:6. Recently, Hindle and Findlay [87] showed that the virus never survived for twenty-four hours if kept at a p_H range of from 3 to 4.

The effect of heat on the yellow fever virus, which was originally studied by Marchoux, Salimbeni and Simond,[20] who found that a

84. Theiler and Sellards (footnote 60).

85. Hoffmann, W. H.: J. Trop. Med. **31**:1, 1928.

86. Blanc, G.; Caminopetros, J., and Giroud, P.: Bull. Acad. de méd., Paris **101**:442, 1929.

87. Hindle, E., and Findlay, G. M.: Brit. J. Exper. Path. **11**:134, 1930.

temperature of 55 C. in five minutes destroyed serum virus, was reinvestigated by Frobisher.[79] He showed that virus-containing serum heated at 60 C. for ten minutes was inactivated, but that heating at 55 C. for ten minutes did not always render it noninfectious. This author also stated that temperatures below 55 C. could not be relied on to inactivate the virus in ten minutes, but that desiccated virus-containing blood heated at 50 C. for ten minutes in one case was able to produce yellow fever in a monkey after a prolonged period of incubation. Virus-containing serum exposed to the air for forty-eight hours loses its virulence, as shown long ago by the French Commission, but surface tension reducents, such as 0.7 per cent sodium oleate and 0.07 per cent hexylresorcinol, have no effect, as reported by Frobisher.[79] The latter also obtained indifferent results with experiments in cataphoresis, but Hindle and Findlay [87] more recently showed that the virus carries a negative charge at a p_H of from 5.2 to 7, and that its iso-electric zone ranges from p_H 4.2 to p_H 5.2.

That the virus of yellow fever is filtrable has been known since the original work of the American Commission, which was confirmed by the French Commission and by Rosenau, Parker, Francis and Beyer.[88] More recently, Stokes, Bauer and Hudson confirmed this work as regards virus contained in serum, but could not filter the virus contained in mosquitos if they used a macerated saline suspension of the insect. However, Sawyer and Frobisher,[89] in repeating the latter work, found that if the macerated mosquitos were suspended in serum rather than in saline solution, the virus would pass the filter.

Marchoux and his collaborators in 1903 showed that if defibrinated human blood containing virus was kept under a petrolatum seal, the virus would remain viable for five, but not for eight days. This work was confirmed by Aragao,[9] who found that the virus in human blood did not survive longer than nine days, if the blood was kept in the icebox, and by Sawyer, Lloyd and Kitchen.[90] The latter showed that the causative agent, when preserved, acts in a manner similar to that of the other members of the group of filtrable viruses. They state that if monkey virus, either of the blood or of the liver, is frozen and dried in vacuo and then kept in a sealed glass container in the icebox, it remains viable for at least 154 days, and if dried in the nonfrozen state, the results are practically the same. Previous to this, Hindle [19] reported that dried virus if kept in vacuo in the icebox would be virulent for at least three months, and Pettit, Stefanopoulo and Kolochine [53] also reported that they preserved their virus on ice, in the form of dried

88. Rosenau, M. J.; Parker, H. B.; Francis, E., and Bergen, G. E.: Bull. Yellow Fever Inst., 1904, no. 14 (published 1905).

89. Sawyer, W. A., and Frobisher, M., Jr.: J. Exper. Med. **50**:713, 1929.

90. Sawyer, W. A.; Lloyd, W. D. M., and Kitchen, S. F.: J. Exper. Med. **50**:1, 1929.

blood. Sawyer and his collaborators [90] showed that if the virus is stored in 50 per cent glycerin, it will remain virulent for 60 days, and viable, but not virulent, for 100 days. Theiler [40] confirmed this work. He found that mouse virus-containing brain kept at from 2 C. to —4 C. in 50 per cent glycerin was viable after 50, but not after 100, days, and that virus containing brain kept at —8 C. survived for at least 160 days.

Cultivation of the Virus.—Since the beginning of the century, when it was shown that the virus of yellow fever was filtrable, no one, except Noguchi [5] and his collaborators, had been able to isolate a visible microorganism until 1929. In that year Kuczynski and Hohenadel [91] claimed to have isolated an organism, *Bacillus hepatodystrophicans,* from cultures of their yellow fever material, which they claimed represented a phase of the life cycle of the virus and produced the typical disease in monkeys and guinea-pigs. Their work is too recent to have received extensive confirmation or denial, but in 1930 da Costa Cruz [92] reported negative results in an attempt to produce yellow fever in monkeys with Kuczynski's bacillus. Da Costa Cruz expressed the belief that the organism belongs to the diphtheroid group. Lewis,[61] whose work showed that the virus could survive in certain mediums for twelve days at 37 C., said that if, as previously mentioned, 0.000,001 cc. of blood could cause an infection in monkeys and if the virus could survive at 37 C. for that length of time, Kuczynski's success could be traced to the fact that he might always have carried over some virus in his subcultures.

No attempts at propagation of the virus in tissue cultures have been reported.

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91. Kuczynski and Hohenadel (footnote 51). Kuczynski, M. H.; Hohenadel, B., and MacClure, E.: Klin. Wchnschr. **8**:1960, 1929; **9**:108, 1930; Tr. Roy. Soc. Trop. Med. & Hyg. **23**:439, 1930.

92. Da Costa Cruz, J.: Compt. rend. Soc. de biol. **102**:610, 1929.

Notes and News

University News, Appointments, Promotions, Resignations, Deaths, etc.—Henry Fraser, formerly director of the Institute for Medical Research, Federated Malay States, has died at the age of 57. He contributed to the knowledge of beriberi and dysentery.

Howard J. Shaughnessy has been appointed chief of the laboratories of the State Department of Public Health of Illinois.

In the department of pathology of Albany Medical College, Kiyoshi Hosoi has been appointed assistant professor and Karl Voldeng Littauer fellow in pathology.

Charles B. McGlumphy has resigned as professor of pathology and bacteriology in the University of North Dakota to become pathologist at the Deaconess Hospital, Evansville, Ind.

At Jefferson Medical College, Philadelphia, Harold L. Stewart has been appointed instructor in pathology and Starling C. Yinger research fellow.

F. W. Konzelmann has resigned as assistant professor in Jefferson Medical College to accept an appointment as pathologist to the Temple University Hospital, Philadelphia.

It is reported that Henry Stuart Willis of the Johns Hopkins University School of Medicine has accepted an appointment as pathologist at the Maybury Sanatorium, Northville, Mich., in the place of Max Pinner.

E. O. Jordan, professor of bacteriology in the University of Chicago, has been elected a member of the board of scientific directors of the International Health Division of the Rockefeller Foundation.

C. W. Muehlberger has been appointed chemist to the coroner's office of Cook County (Chicago), thus succeeding the late Ralph W. Webster.

Supplement III of *Acta pathologica et microbiologica scandinavica,* is issued in honor of Thorvald Madsen's sixtieth birthday. This supplement also constitutes volume 20 of *Communications de l'Institut sérothérapique de l'État Danois.*

Hedley Duncan Wright, reader in bacteriology in the University of London and assistant editor of the *Journal of Pathology and Bacteriology,* has been appointed to the chair of bacteriology in Sydney University.

Alvin E. Belden, William F. Lawrence and Edna E. Nicholson are announced as the successful candidates for the research fellowships of the National Tuberculosis Association for 1930-1931.

In the University of California, Charles L. Connor has been promoted to professor of pathology and Max S. Marshall to associate professor of bacteriology.

Society News.—At the meeting of the American Medical Association in Detroit, G. Novy and Malcolm H. Soule were awarded a gold medal for an exhibit illustrating respiration and dissociation of bacteria.

At the recent meeting of the American Association for the Study of Goiter at Seattle, William F. Rienhoff, Jr., of Johns Hopkins University, Baltimore, received the annual award of $300 for the best essay dealing with the problem of goiter.

Matheson Foundation.—The income of $600,000 bequeathed by the will of William J. Matheson will be used largely for the support of medical research. It is reported that the study of epidemic encephalitis, an international survey of which was provided for by Dr. Matheson in 1927, will be continued.

Ward Burdick Research Gold Medal.—This medal, which is presented annually by the American Society of Clinical Pathologists for the outstanding piece of research done by one of its fellows, was awarded this year to H. J. Corper, Denver, for his work on isolating and culturing the tubercle bacillus. Dr. Corper was also made president-elect of the American Society of Clinical Pathologists at the recent convention in Detroit.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE TIME OF OVULATION AS CHECKED BY THE RECOVERY OF OVA FROM THE FALLOPIAN TUBES. Q. U. NEWELL, EDGAR ALLEN, J. P. PRATT AND L. J. BLAND, Am. J. Obst. & Gynec. **19**:180, 1930.

The authors describe a method for collecting ova by irrigating fallopian tubes at laparotomy, which they recommend as being likewise useful in determining the tubal patency. Ninety patients were selected for operation at a time in the menstrual cycle shortly after ovulation. The latter was estimated to occur on the twelfth or thirteenth day after the onset of the last menses. Five ova were identified when sectioned, and their morphology will be described in detail.

A. J. KOBAK.

ANTERIOR HYPOPHYSIS IN THE PREGNANT AND NONPREGNANT STATES. A. R. BACON, Am. J. Obst. & Gynec. **19**:352, 1930.

Although Ascheim and Zondek have demonstrated an increased amount of hormone in pregnant women which they believe arises from the anterior hypophysis, Bacon's work does not entirely support this. The latter, on the assumption that if the theories of the former were correct, has compared grafts of fresh pituitary glands of pregnant and nonpregnant cattle, in infantile mice. *A priori*, if the views of Ascheim and Zondek are correct, smaller grafts from pregnant cattle should suffice in producing estrus-like changes in the engrafted animals. Bacon did not find this, and in fact the hypophyses of pregnant cattle were somewhat poorer in their hormone content. Two possible conclusions can be made from these experiments, namely, that the hormone hypophyses is not the sole seat of the formation of hormone, and that perhaps a different mechanism of hormone factors prevails in cattle.

A. J. KOBAK.

THE ACTION OF HISTAMINE ON THE BRONCHIOLES AND PULMONARY VESSELS OF THE GUINEA-PIG. M. E. FIELD and C. K. DRINKER, Am. J. Physiol. **93**:138, 1930.

The vasoconstriction of the pulmonary vessels and the bronchoconstriction that follow the injection of histamine could be readily separated only by the use of very small quantities, with which there was obtained a rise of pulmonary pressure without bronchial constriction. The latter phenomenon was obtained with doses of from 0.0001 to 0.01170 mg. of histamine per kilogram of body weight; the former alone, with doses ranging from 0.000093 to 0.00310 mg. per kilogram.

H. E. EGGERS.

THE INFLUENCE OF INORGANIC IRON ON THE ANEMIA OF RICE DISEASE IN PIGEONS. O. W. BARLOW, Am. J. Physiol. **93**:156, 1930.

The anemia that develops in pigeons on a polished rice diet as the result of the deficiency in vitamins was not affected by the addition to the diet of inorganic iron in the form of ferrous carbonate in amounts ranging from therapeutic to toxic dosages. Actually this anemia does not appear to be due to any deficit of iron in the body, as it is associated with considerable increase in the disposition of hemosiderin in the liver. Since this same effect is shown, though to a less degree, by fasting birds, inanition is to be regarded as at least one causative factor. Remedy of all the known deficiencies of the polished rice diet is without effect on the disease picture, except that of a deficiency in vitamin B, a deficiency which appears to be the single primary causative factor of the disease.

H. E. EGGERS.

THE INFLUENCE OF VITAMIN B ON THE INANITION ANEMIA AND BACTERIEMIA OF RICE DISEASE IN PIGEONS. O. W. BARLOW, Am. J. Physiol. **93**:161, 1930.

The several phenomena of rice disease in pigeons—loss of weight, anemia and bacteremia—which show a definite parallelism, are not due to the rice diet as such; for they may be duplicated, even exaggerated, by the feeding of any synthetic diet free from vitamin B. Individual pigeons vary in their requirement of vitamin B, and with normal animals voluntary starvation plays a large part in this variation; previous fasting or inanition resulting from previous vitamin B deficiency increased the amount of the vitamin necessary to restore the balance in weight or blood picture. While there is a sufficiently close parallelism between bacteremia and the development of anemia to suggest a possible causal relationship between the two, there are enough divergences to suggest the operation of other factors as well. Addition of lactose to the deficient diet affected both the bacteremia and the anemia favorably, possibly in part by the lessening of intestinal toxemia.

H. E. EGGERS.

THE EFFECTS OF X-RAYS ON THE ADRENAL GLAND. F. T. ROGERS and C. L. MARTIN, Am. J. Physiol. **93**:219, 1930.

In dogs with one suprarenal gland excised, the direct application of the x-rays with an intensity estimated as three and one-half times the erythema dose in man was without any effect on the remaining gland except for causing a slight fibrosis. There was no functional disturbance during a period of observation of from three to twelve months. Application of from six to eight doses was without observable functional effect for three months. With excessive doses, symptoms of suprarenal deficiency appeared gradually after a lapse of several months, with a gradual onset of muscular weakness, depression of metabolism and terminal lowering of blood chlorides. In the exposed gland, a heavy dosage of the x-rays caused degenerative changes, which appeared first in the medulla and then in the cortical portions, with an extensive diffuse fibrosis.

H. E. EGGERS.

POISONOUS FISHES AND FISH POISONINGS, WITH SPECIAL REFERENCE TO CIGUATERA IN THE WEST INDIES. E. W. GUDGER, Am. J. Trop. Med. **10**: 43, 1930.

Certain poisonous fishes have developed spines for stinging or laceration, and in connection with these stings have developed glands secreting poisons. These are comparable to the fangs and poison glands of venomous snakes, and like them function as protective devices. Probably, also, these glands, like those of the snakes, have by a perversion of metabolism been developed out of what would normally have been perfectly harmless organs. Such fishes poison men only when they sting them. Comparable is the poisoning which comes from the injection of the blood serum of a fish into the blood stream of a mammal and, by inference, of a man. As already indicated, this is an experimental operation and is of no concern here.

Finally, there is the fish poisoning by ingestion of the muscular or other tissues of the fish, the ciguatera of the West Indies. Here we have undoubtedly two forms of poisoning—that by ptomaines formed in the partially decomposed tissues of the fish, and that by toxins secreted in various organs but particularly in the ovaries and less notably in the testes at the breeding season. In the literature, as in ordinary medical practice, the two kinds of poisoning are almost hopelessly entangled.

From what has been said, it is clear that in the disease called ciguatera there is an interesting, and, so far as the West Indies are concerned, an almost virgin field for investigations by modern clinical and chemical procedure for the differentiation of these two kinds of poisoning, and for putting the treatment on a sound scientific basis.

AUTHOR'S SUMMARY.

THE PHYSIOLOGIC EFFECT OF NONLIVING TESTIS GRAFTS. CARL R. MOORE, J. A. M. A. **94**:1912, 1930.

The spermatozoon motility test provides a means of revealing the presence of testis hormone in guinea-pigs for periods as short as ten days; yet by means of this test it has been impossible to detect any hormone liberated from two autoplastic grafts of whole testis in subcutaneous pockets.

In the rat, a cytologic study of the prostate gland and seminal vesicles affords dependable methods of detecting the absence of hormone for periods of from three to five days. Here, also, two autoplastic grafts of whole testis in subcutaneous pockets failed to delay the onset of castration changes for as short a period as two days.

The autolysis of nonviable testicular grafts does not liberate hormone in amounts that can be detected by any means at present known. Furthermore, the testis hormone is not stored within the body, but is excreted by the kidneys. A continuous supply is necessary to maintain the secondary sex characters in a normal condition.

There is no known acceptable evidence that nonviable testicular grafts, i. e., grafts that fail to incorporate with the body and actively secrete, exert any immediate or remote beneficial effect on the host organism.

AUTHOR'S SUMMARY.

TISSUE METABOLISM (THE RESPIRATORY QUOTIENT OF NORMAL AND DIABETIC TISSUE). HENRY B. RICHARDSON, EPHRAIM SHORR AND ROBERT O. LOEBEL, J. Biol. Chem. **86**:551, 1930.

The rate of oxidation in excised renal or muscular tissue of the dog varies within narrow limits, and is about the same as is found in the intact organ in situ. The respiratory quotients of normal tissues are intermediate between 1 and 0.7, and imply the participation of fat in the oxidation. The average respiratory quotient of renal or muscular tissue taken from depancreatized dogs was 0.7 to 0.75, indicating either no oxidation of carbohydrate, or at most a small amount. These observations conflict with the theory that carbohydrate is essential as the immediate fuel for muscle and with that theory of diabetes which holds that the waste dextrose originates from fat.

AUTHORS' SUMMARY.

NATURE AND RÔLE OF FATTY ACID ESSENTIAL IN NUTRITION. G. O. BURR and M. M. BURR, J. Biol. Chem. **86**:587, 1930.

In the rat, fat-free diets produce extensive, even fatal, renal degeneration. The disease resulting from fat-free diet is not cured by saturated fatty acids but by linoleic acid, either pure or in olive oil, lard, corn oil, egg lecithin, etc. The important conclusion is reached that linoleic acid is essential in nutrition.

HETEROGENOUS LEUKOCYTES AS A VEHICLE FOR THERAPEUTIC AGENTS. P. SPANIER, Beitr. z. Klin. d. Tuberk. **73**:210, 1929.

Dead cells and heterogenous cells are retained and destroyed in the lungs. If heterogenous leukocytes are introduced into the venous system, they are retained in the lungs. Since leukocytes can absorb certain therapeutic agents, it is possible to use heterogenous leukocytes as vehicles for therapeutic material. It is expected that, thus administered, therapeutic material may come in closer contact with pulmonary lesions and may be retained there for a longer time than with the usual modes of administration.

MAX PINNER.

Pathologic Anatomy

VARIX OF THE UMBILICAL CORD. FRED L. ADAIR and R. E. MCDONALD, Am. J. Obst. & Gynec. **17**:836, 1929.

The case reported is one of ruptured umbilical varix and adds one to the four cases which the authors found recorded.

A. J. KOBAK.

NODULAR FIBROSIS OF THE SPLEEN ASSOCIATED WITH FILARIA LOA. OSKAR KLOTZ, Am. J. Trop. Med. **10**:57, 1930.

Groups of microfilariae aggregate in the spleen of some cases of infection caused by *Filaria loa*. These areas of localization are associated with an inflammatory reaction and fibrosis. A tissue eosinophilia accompanies the filarial inflammation. These reactions in the spleen may be analogous to the external chronic Calabar swellings.

AUTHOR'S SUMMARY.

GIANT CELL TUMORS OF THE SPINE. J. V. SANTOS, Ann. Surg. **91**:37, 1930.

Laminectomy on a white man, aged 27, revealed a dark purple mass on the dorsal aspect of the dura mater extending from the second lumbar to the twelfth thoracic vertebra and into the surrounding muscles. This case represents the twenty-third of giant cell tumor, which were most frequent in the lumbar region, although the cervical and dorsal vertebrae may also be involved.

RICHARD A. LIFVENDAHL.

SARCOMA OF THE THYROID GLAND. I. Arons, Ann. Surg. **91**:44, 1930.

A 3.5 cm. node in the right lobe of the thyroid gland was found in a patient, aged 58, who had a paralysis of the recurrent laryngeal nerve but no evidences of hyperthyroidism. The microscopic picture was that of fibrosarcoma. From the literature, it is recorded that pressure effects on the surrounding anatomic structures are not unusual and that metastases have occurred in the bones, intestines, liver, kidney, lung and regional lymph glands.

RICHARD A. LIFVENDAHL.

CHANGES IN THE INTRAHEPATIC DUCTS FOLLOWING CHOLECYSTECTOMY. J. E. SUTTON, JR., Ann. Surg. **91**:65, 1930.

Fifteen days following the removal of the gallbladder in dogs the intrahepatic ducts showed epithelial disintegration, stratification of the epithelial cells, bud formation and epithelial exfoliation. Forty days after operation there were folds projecting as villous-like structures and high columnar epithelium similar to that of the wall of the gallbladder instead of the low columnar epithelium, as normally lines the ducts.

RICHARD A. LIFVENDAHL.

ON THE FORMATION OF EPITHELIOID AND GIANT CELLS. R. S. CUNNINGHAM, E. H. TOMPKINS and J. S. LAWRENCE, Bull. Johns Hopkins Hosp. **46**:323, 1930.

The subcutaneous injection of guinea-pigs with olive oil containing yellow phosphorus caused the production of large numbers of typical epithelioid and giant cells, which were indistinguishable from those in tuberculous lesions.

AUTHORS' SUMMARY.

STUDIES ON VITAL STAINING. H. P. SMITH, J. Exper. Med. **51**:379, 1930.

Brilliant vital red injected into the blood stream of dogs is slowly taken up by phagocytes in various parts of the body, but eventually an equilibrium is established, after which the concentration as measured in the plasma remains almost

constant for long intervals of time. This equilibrium can be disturbed by injecting more dye, and in this case the phagocytes resume ingestive activity, apparently with normal or nearly normal vigor. This activity continues until a rather large part of the newly injected dye has been removed, and as the reaction again slows up, one notes that both plasma and tissues contain more dye than before. It is difficult to be certain that the distribution ratio of dye between plasma and tissues remains unaltered with dosage, but evidence indicates that for nontoxic doses, at least, that is approximately true. This study of this partition ratio is complicated by the fact that the liver slowly excretes dye into the bile and this helps to reduce the amount of dye in the body. Partial correction for this factor can be made by ascertaining the output of dye in dogs with a biliary fistula. The latter studies show that elimination of dye into bile is relatively less efficient when large doses of dye are given to the animal than with smaller dosage. This undue retention of dye in the body with large dosage helps to maintain the dye concentration in the plasma at unduly high levels. These peculiarities in excretion of the liver have an important bearing on the physiology of that organ in general, and in addition they also have an important application in connection with the theory of "blockade of the reticulo-endothelial system." It is now obvious that prolonged retention of dye in the blood stream does not of itself prove that this group of phagocytic cells is "blocked" against the entrance of foreign material. Altered excretion by the liver, kidney, etc., must be ruled out before one can accept such data as evidence of "blockade."

AUTHOR'S SUMMARY.

STUDIES ON VITAL STAINING. H. P. SMITH, J. Exper. Med. **51**:395, 1930.

When large amounts of brilliant vital red are injected into the blood stream of dogs, the dye is gradually removed from circulation, and most of it is deposited in numerous phagocytic cells which are scattered throughout various organs and tissues. The dye occurs largely in the form of tiny red granules crowded together in the cytoplasm of these cells. If Niagara sky blue, a closely related dyestuff, is injected, it too is taken up and stored in these same cells. It is shown that the presence of red dye in the tissues does not inhibit the cells from taking up the blue one. The normal ability of the phagocytes to take up Niagara sky blue is observed also when this dye is injected simultaneously with brilliant vital red. This normal response toward the blue dye is seen even though the phagocytes are busied at the same time in the process of engulfing and storing the red dye. These experiments show that it is difficult if not impossible to "block" the cells with one dye so that their ability to take up another is even slightly impaired. The two dyes employed in these studies are shown to be particularly suitable for experiments of the sort here reported.

AUTHOR'S SUMMARY.

CONGENITAL DISLOCATION OF THE HIP. H. A. T. FAIRBANK, Brit. J. Surg. **17**: 380, 1930.

The study was founded on thirty-five museum specimens, comprising forty-six dislocated hips and fifty open operations. The primary fault was found to be the poor development of the upper margin of the acetabulum, including malformations of the cotyloid ligament, the cartilaginous margin and even the bone. As the condition progresses the acetabulum later assumes a triangular shape with a sharp, straight and not uncommonly undercut edges, the cavity being filled by cartilage or fibrofatty tissue. Secondary changes include a triangular outline of the obturator foramen and an increase in the public angle; the ilium is shorter and broader than normal, and a false acetabulum forms on the dorsum ilii which may be located high, low, anteriorly or close to the sciatic notch. The tuber ischii shows roughening and thickening of the bone. The femoral head is smaller than normal, though relatively larger than the acetabulum, and is flattened on its inner and posterior aspects with erosion and lipping in adults. The femoral neck is usually longer and more slender

than normal and is associated with varying degrees of coxa vara. The capsule migrates upward, blends with the periosteum of the acetabulum and becomes thickened. The ligamentum teres is frequently absent in cases of long standing.

RICHARD A. LIFVENDAHL.

SPONTANEOUS RUPTURE OF THE NORMAL SPLEEN. H. BAILEY, Brit. J. Surg. **17**:417, 1930.

A large subcapsular hematoma of the spleen was found in a white man, aged 20, who presented no history of an injury. The microscopic picture of the organ was normal.

RICHARD A. LIFVENDAHL.

A REMARKABLE MECKEL'S DIVERTICULUM. H. B. YATES, Brit. J. Surg. **17**:456, 1930.

In a woman, aged 37, who was three months pregnant, was found a huge tumor mass that filled the entire right side of the abdomen, and was covered by peritoneum on the anterior aspect and the right side. The posterior surface was located directly on the posterior abdominal wall. It is described as a rising 8 cm. proximal to the ileocecal valve, forming a huge diverticulum, the walls of which, microscopically, presented the picture of the ileum, except that the muscles were hypertrophied and there was very little lymphoid tissue. The contents consisted of brown fecal material.

RICHARD A. LIFVENDAHL.

STRANGULATED INTERNAL HERNIA IN A RETRO-APPENDICULAR PARACECAL POUCH. C. DONALD, Brit. J. Surg. **17**:463, 1930.

A partially collapsed, hernial pouch, 10 by 9 cm., was found on the inner side of the ascending colon just above the ileocecal junction extending to the line of attachment of the mesentery proper. Its anterior wall was thin and vascular, and fused to it posteriorly was the appendix which was pointed toward the spleen. The cecum was not fixed posteriorly, the pouch being located on its inner border. This sac contained 16 inches (40-64 cm.) of congested ileum. The hernia was associated with an ileo-appendicular fossa of funnel shape, with the fold running from the terminal 2 inches (5 cm.) of the ileum to the appendix itself, losing itself on the anterior margin of the hernial opening. The other fossae of this region and the embryologic aspects are discussed.

RICHARD A. LIFVENDAHL.

A SOLITARY PLASMA-CELLED MYELOMA. H. ROGERS, Brit. J. Surg. **17**:518, 1930.

A tumor, 4½ by 2¼ inches, with a honeycombed appearance, led to the spontaneous fracture of the right femur in a white man, aged 34. There was a cavity filled with a soft, white material which consisted, for the most part, of plasma cells. Reexamination of the same material during the two following operations showed only a structural matrix or well formed fibrous tissue or vascular granulation tissue.

RICHARD A. LIFVENDAHL.

THYROID METASTASIS IN BONE. W. K. CONNELL, Brit. J. Surg. **17**:523, 1930.

In two women, aged 45 and 50, respectively, a large tumor mass was noted in the occipital region. Microscopic examination revealed a fetal type of adenoma. In the thyroid gland of each patient there was a walnut and a hen's egg sized mass. From the literature it was noted that the bones, particularly the sternum, vertebrae, ribs, humerus, femur, pelvis and clavicle, are the structures most frequently involved. When occurring in the cranial bones, the metastases tend to follow the suture lines.

RICHARD A. LIFVENDAHL.

GENERALIZED OSTEITIS FIBROSA WITH PARATHYROID HYPERPLASIA. A. M. DRENNAN, J. Path. & Bact. **33**:65, 1930.

A case is recorded of osteitis fibrosa with cystic changes in the bones and a large mass of parathyroid tissue. The bone changes consist of absorption of existing trabeculae replacement of preexisting bone by fibrocellular tissue, with or without calcification of this tissue, and formation of osteoid tissue and new bone. In places where loss of original bone is marked, e. g., in the lower end of the tibia, areas of hemorrhage occur with invasion by fibrocellular tissue and giant cells (osteoclastic type), giving rise to the so-called cystic areas, although many of these are really solid masses but deficient in bone tissue. The distribution of all these changes is general throughout the skeleton, but the type of change in any part varies considerably, e. g., tibia as compared with humerus or with skull. As already mentioned, the bony changes in this case are exactly the same as those described in the case of Dawson and Struthers. There is nothing in the history to suggest a cause for the condition. The thyroid changes are degenerative and are unlikely, per se, to have any relation to the bone disease, as changes of this type are often found unassociated with any bone lesions. The failure to find normal parathyroids is interesting. The mass of abnormal parathyroid tissue present in the position of the right lower parathyroid would seem to be either tumor growth or hyperplasia of the preexisting gland to compensate for the absence or loss of the other parathyroids. In Dawson's case, the parathyroid mass was regarded as an adenoma of parathyroid. The mass in this case seems to be similar as far as gross and microscopic appearances show. As pointed out by Vines (1924), Korenchevsky (1922) and others, the relation of the parathyroids to calcium metabolism is still obscure, but the effect of their absence would appear to be somewhat similar to the effect of deficiency of vitamin A and of calcium. Conversely, enlargement of the parathyroids has been observed in rickets and osteomalacia by many authors. Unfortunately, the data in any one case of disease are frequently deficient; in this case there is no record of calcium intake or output, and no chemical examination of the blood or organs was attempted. Therefore, only morphologic data are recorded.

AUTHOR'S SUMMARY.

MILIARY ANEURYSMS IN THE BRAIN. F. H. K. GREEN, J. Path. & Bact. **33**:71, 1930.

A technic is described for the search for miliary aneurysms in the brain. During an examination of the brains of ten arteriosclerotic subjects only three undoubted "miliary aneurysms" were found. One of these could not be classified from the few sections obtained; the other two were shown to be respectively saccular (or dissecting) and fusiform. Each arose from a grossly diseased parent trunk. Two of these aneurysms had ruptured, giving rise to small hemorrhages in the brain substance. The third was completely thrombosed and lay in relation to a zone of ischemic softening. It is suggested that miliary aneurysms only arise where atheroma involves the media of an artery to an extreme degree. The process responsible for the production of "saccular" aneurysms would appear to be a stretching and rupture of the necrotic intima and media leading to effusion of blood into the Virchow-Robin space, and followed by condensation and distention of the adventitia. The latter may undergo secondary rupture, and so give free communication between the lumen of the parent artery and the surrounding tissues. In this way miliary aneurysms may be responsible for some cases of cerebral hemorrhage. Complete thrombosis of miliary aneurysms may cause foci of ischemic softening in the brain.

AUTHOR'S SUMMARY.

THE PATHOLOGY OF DISSEMINATED ENCEPHALOMYELITIS OF THE DOG (THE "NERVOUS FORM OF CANINE DISTEMPER"). J. R. PERDRAU and L. P. PUGH, J. Path. & Bact. **33**:79, 1930.

Demyelination of the type commonly found in subacute disseminated sclerosis was found in four of fourteen cases of disseminated encephalomyelitis of the dog

(the "nervous form of canine distemper"). The parts of the central nervous system where demyelination was most commonly found were the cerebellar peduncles and adjacent portions of the cerebellum and of the brain stem. Distemper is not apparently an essential antecedent of the encephalomyelitis, as the association of the two conditions was noted in only seven of fourteen cases observed. The time interval which has been recorded in the disseminated encephalomyelitis of man between the onset of the acute infection and the appearance of the nervous phenomena is fairly constant; this has no parallel in this condition of the dog where it varies widely from case to case.

AUTHORS' SUMMARY.

THE LATE RESULTS OF INTRAVENOUS INJECTION OF COLLOIDAL IRON. D. F. CAPPELL, J. Path. & Bact. **33**:175, 1930.

Colloidal iron injected intravenously is taken up first by certain cells belonging to the reticulo-endothelial system and by certain of the circulating leukocytes in the same way as suspensoid substances, e. g., carbon is. Later, the iron undergoes transformations which result in its redistribution. The most important of the later changes is believed to consist in the entry of iron into some compound—possibly a loose combination with the plasma proteins; and it is probable that this linking is brought about through the activity of reticulo-endothelial cells. This loosely bound iron is capable of passing through capillary walls, and thus iron storage appears later in lymphatic glands and in the parenchyma cells of the liver and kidney. In the mouse, the liver, spleen and lymphatic glands are the most important sites of iron storage, and of these the liver contains the greatest amount of iron in the later stages. Excess iron administered parenterally is dealt with similarly to excess iron derived from hemolysis occurring in the circulation. It is important that no ill effects follow massive accumulation of iron in the liver cells. The pancrease does not participate in the storage of iron. Accordingly, nothing analogous to the lesions of hemochromatosis in the human subject has been observed in the organs of animals subjected to excess iron over prolonged periods.

AUTHOR'S SUMMARY.

PRIMARY DIFFUSE ENDOTHELIOMA OF SOFT MENINGES. S. S. VAIL, Virchows Arch. f. path. Anat. **273**:441, 1929.

A man, aged 30, suffered from increasing headaches, vomiting and attacks of unconsciousness; became blind, and psychosis of the schizophrenic type developed. At autopsy, diffuse thickening of the soft meninges was found, with dense yellow layers along the fossae Sylvii. The gross diagnosis was chronic leptomeningitis. Microscopically, the whole brain was covered by strands of homogeneous round ovoid cells, which partly surrounded the blood vessels. The brain substance was invaded.

ALFRED PLAUT.

MULTIPLE MALFORMATIONS IN A HYPOPLASTIC PERSON. VOJIN LAZAREVIĆ, Virchows Arch. f. path. Anat. **273**:445, 1929.

An idiotic girl, aged 13 years, had a family history that was irrelevant. There were five other healthy children. At the age of 3 paralysis of the left arm and leg developed. She often choked while eating; palpitations were always present; menstruation had not begun. The clinical diagnosis was: spastic infantile hemiplegia, mitral insufficiency and stenosis, defect of septum. Death occurred from cerebral embolism. The antomic diagnosis was: primary microgyria of the right cerebral hemisphere; defect in the septum of the ventricles and auricles, congenital insufficiency of the venous ostia; thymus persistens; hypoplasia of the arteries; hyperplasia of the lymphatic apparatus; extensive polyposis adenomatosa of the large intestine; abnormal lobulation of the right lung, liver, spleen and kidneys; large ovaries with follicular cysts; pigmented nevi of the skin.

ALFRED PLAUT.

IDIOPATHIC NECROSIS IN THE MEDIA OF THE AORTA. J. ERDHEIM, Virchows Arch. f. path. Anat. **273**:454, 1929.

This disease is characterized by necrosis in the media without any inflammatory reaction. The picture originally was mistaken for syphilitic aortitis without accompanying arteriosclerosis. Defects in the media are seen through the intact, hence transparent, intima; they may be compared to striae gravidarum, but they are never purplish as in aortitis syphilitica—they are gray. The wall becomes thin, and rupture may take place. At the edge of such a lesion, defects in the elastic lamellae are found; the lamellae themselves may be preserved but without elastin. The defects appear red in the van Gieson stain. Cavities form, sometimes containing coagulated material; the muscle tissue disappears to a greater or lesser extent. True necrosis may occur. Inflammation is entirely absent.

Nearer the center of a lesion necrosis prevails in the outer layers, partly with coalescing but well stained elastic lamellae. If one does not pay attention to the staining of the nuclei, one can easily overlook the necrosis. In spots the tissue of the media is completely supplanted by connective tissue. The necrotic material disappears slowly; in the inner layers it disappears more rapidly, probably carried off by the blood stream. There is very little regeneration. Nearer the intima, rarefaction of elastic layers is found without necrosis; later the muscle tissue disappears. Thus the process in the innermost layers of the media is different from that in the outer strata. The intima is thickened and contains newly formed muscle cells.

The complete absence of inflammation forces one to assume an entirely "humoral" removal of the necrotic material. The cause for the absence of inflammation, as well as the etiology of the whole disease, is unknown. Different toxic factors have been mentioned. The disease was unknown before the World War.

ALFRED PLAUT.

NIEMANN-PICK DISEASE (LIPOIDOCELLULAR SPLENOMEGALY). H. SMETANA, Virchows Arch. f. path. Anat. **274**:697, 1930.

In a first born Jewish girl, enlargement of the liver was noted at age of 3 months together with increasing brownish discoloration of the skin. The blood was normal. At the age of 20 months, the child could not sit and was unable to support her head. She was idiotic, but not blind. The spleen was much enlarged. Death occurred from pneumonia. Autopsy showed soft, edematous meninges and a firm brain with thick convolutions somewhat similar to a brain in familiar amaurotic idiocy; a firm spleen (222 Gm.), reddish-white pulp; yellowish intestinal mucosa and mesenteric lymph nodes; reddish-yellow marrow of the femur, and a firm, yellowish-gray liver (1,140 Gm.).

Large, vacuolized cells from 20 to 60 microns in diameter were found in all the organs, most of them having one nucleus. They were numerous in the spleen, liver, lung, thymus, lymph nodes and brain. With sudan III stain, all colors from light yellow to brown red were found. With the Smith-Dietrich stain, gray to black granules were found in all the cells. Doubly refractive material was present in large amount in the thymus, bone-marrow and lymph nodes, and small amounts in the ovaries, intima of the aorta and perivascular tissue in the brain. The liver and spleen contained no doubly refractive material. In the liver, the large cells protruded into the capillaries, endothelial cells separating them from the liver cells. All transitions from normal Kupffer cells, containing a few vacuoles, to the large, completely vacuolized cells, were traced. In the lungs the large cells contained up to twenty nuclei and occasionally large fat droplets. It is possible that large amounts of the lipoid material resulting from the breaking down of the large cells in all the organs, were carried into the lung and thus were responsible for the different appearance of the large cells in the lungs.

Chemical examination of fresh liver, spleen and brain showed much increase in lecithin and phosphorus-containing lipoids. No kerasin could be found. The chemical examination is the best means of differentiating between Gaucher's disease

in infants and Niemann-Pick's disease. For the Smith-Dietrich stain the author recommends mordanting and staining in bulk, followed by celloidin embedding and differentiation under the control of the microscope.

ALFRED PLAUT.

EXPERIMENTAL STEATOSIS OF THE EYE OF THE CHICKEN. T. UCHIYAMA, Virchows Arch. f. path. Anat. **274**:803, 1930.

The cholesterol content of the blood varies much in the chicken and more so in hens. A detailed description is given of the distribution of fat substances in different parts of the cock's eye under normal conditions and after feeding cholesterol oil. No true senile arcus could be produced. The distribution of the fat substances is different from that in man or rabbit.

ALFRED PLAUT.

UNIVERSAL CONGENITAL HYDROPS. H. HARTMANN, Zentralbl. f. Gynäk. **52**:299, 1928.

Hydrops congenitus is characterized by anasarca, hydrops of all cavities and myeloid foci in liver, spleen, kidney, suprarenal gland and intestine. The etiology is unknown. Syphilis is not the cause, but may produce similar changes. The frequent coincidence of congenital hydrops with maternal nephritis points to the existence of an etiologic connection between these conditions. A toxemia for which the fetus is probably responsible is regarded as the primary cause.

W. C. HUEPER.

THE HISTOLOGIC DIAGNOSIS OF CERVICAL EROSION. H. U. HIRSCH-HOFFMANN, Zentralbl. f. Gynäk. **52**:2013, 1928.

The histologic changes present in the healing stage of a true cervical erosion may resemble closely carcinomatous conditions. Masses of more or less undifferentiated squamous epithelial cells may replace the columnar epithelium of the cervical glands and may fill partially or entirely the glandular lumen. A positive mucin reaction indicates the origin of these benign epithelial formations. The presence of an inflammation may cause a certain degree of irregularity of the epithelial cells. A correct diagnosis requires great experience.

W. C. HUEPER.

SQUAMOUS EPITHELIUM IN HYPERPLASTIC ENDOMETRIAL GLANDS. O. HINTZE, Zentralbl. f. Gynäk. **52**:2209, 1928.

Small circumscribed areas of stratified squamous epithelium growing in nests or strands were found in nine cases of hyperplastic mucosa of the corpus uteri or in glandular polyps. The squamous epithelium was present in glands, replacing the cylindric epithelium, forming sproutlike projections, or filling the lumen completely. These formations are apparently rare, if one considers the large material of the clinic in Berlin and the fact that these nine cases represent the total number observed during a five-year period. As their benign character is not generally recognized, Hintze points to the fact that in four of his cases the patients remained well after a simple curettage.

W. C. HUEPER.

THE KIDNEY DURING PREGNANCY. W. NONNENBRUCH, Zentralbl. f. Gynäk. **53**:514, 1929.

During pregnancy there may be a special, diffuse type of lipoid nephrosis (glomerulonephrosis) in which mainly the epithelium of the main tubules and especially of the glomeruli shows degenerative changes. The inflammatory reaction is by far less marked. Increase of nuclei is in general absent. Blood is usually not present in the urine. The cause is either a direct effect of a toxic substance on the kidney, a conception supported by the occurrence of hemoglobin casts, or

the nephrosis is due to an ischemia of the glomeruli on account of arteriolar spasms. Capillary microscopy shows the existence of spasm in the arterial branch, a factor considered as the cause of the hypertension in nephrosis of pregnancy. Arteriolar spasm is also present in eclampsia affecting the vessels of the brain. Eclampsia is not produced by the existing dyscolloidosis and cholesteremia of the blood. The edematous fluid in eclampsia is almost free from albumin and rich in sodium chloride. The edema may be caused by circulatory disturbances. The function of the kidney is not, or only slightly, impaired in the nephrosis of pregnancy. Absolute rest and a nonirritating dry diet are recommended as a therapeutic measure. The intake of liquids has to be restricted. Large bleedings are well tolerated, but subsequent injections of solutions of sodium chloride are contraindicated. Dextrose has to take the place of sodium chloride.

W. C. Hueper.

Pathologic Chemistry and Physics

The Calcium in the Serum in Jaundice. A. M. Snell, C. H. Greene and F. Wales, Am. J. Physiol. **92**:630, 1930.

In clinical cases of jaundice there was found a slight decrease of serum calcium, probably without significance to the patient. No significant disturbance was found in either the amount or the proportion of diffusible calcium, nor was there any correlation between either total or diffusible calcium and either serum bilirubin or prolongation of clotting time. There evidently is no clinically significant change in the relations of blood calcium during jaundice.

H. E. Eggers.

Chemical Determination of the Glycogen Ratio in the Bundle of His and the Cardiac Muscle in Man and in the Horse. Wallace M. Yater, Arnold E. Osterberg and Hans W. Hefke, Arch. Int. Med. **45**:760, 1930.

The ratio of the percentage of glycogen in the muscle to that in the tissues of the conduction system was determined by a new microchemical technic in twenty-one hearts of human beings and in four hearts of horses. The ratio of the percentage of glycogen in the muscle to that in the bundle of His of the hearts of human beings varied between 1 : 0.50 and 1 : 1.17, with the probable average ratio of 1 : 0.9. The ratio of the percentage of glycogen in the muscle to that in the radicles of the left bundle branch of the hearts of horses varied from 1 : 1.95 to 1 : 10.10, in spite of the much greater fibrous tissue content of the tissues of the conduction system in the horse. Why there should be such a difference in this ratio between the heart of the human being and the heart of the horse cannot be explained at present. Glycogen disappears slowly both from the cardiac muscle and from the tissues of the conduction system in specimens that are first studied within a half hour after death (hearts of horses), but the percentage of glycogen in the hearts (both of human beings and horses) varies markedly without any ascertainable reason.

Authors' Summary.

The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice. Lewis Gunther and D. M. Greenberg, Arch. Int. Med. **45**:983, 1930.

The indirect method of calcium replacement therapy in jaundice should be discarded as a means of proof that the diffusible calcium is low in jaundiced patients, since a direct analytic method is available for the measurement of the diffusible calcium. Analytic studies of the blood of jaundiced patients show that there is no deficiency in the diffusible calcium of the blood serum, regardless of the degree of jaundice between icteric indexes of 17.5 and 200, and regardless of

the absence or presence of abnormal bleeding phenomena. The serum albumin may be low in jaundice. The nondiffusible fraction of the serum calcium may be low as a result of the fall in the serum albumin. The value of the diffusible calcium of the blood serum is a more accurate measure of the physiologically available calcium than the value of either the nondiffusible or the total calcium. Factors other than the amount of available calcium, as measured by the concentration of the diffusible calcium, must be sought to explain the abnormal bleeding phenomena seen in jaundiced patients.

AUTHORS' SUMMARY.

WATER CONTENT OF INTERVERTEBRAL DISKS. JOHANNA PÜSCHEL, Beitr. z. path. Anat. u. z. allg. Path. **84**:123, 1930.

Since the shock-absorbing properties of the intervertebral disks probably depend largely on the water content of the tissue, the author undertook an investigation of the latter at the suggestion of Schmorl, in whose institute a necropsy usually includes the removal of the vertebral column and of one or both femurs. The water content was estimated separately for the annulus fibrosus and nucleus pulposus by determining the loss of weight after drying to constant weight at 103 C. A preliminary investigation having shown no appreciable differences in the water content of the various disks of the same person, the determination was limited to four disks in each case, usually the third and tenth thoracic and the first and fifth lumbar. Twenty-two cases in which the disks revealed no gross changes and four in which alterations were visible to the naked eye were included in the investigation. The water content is highest at birth, having an average value of 78 per cent for the ring and 88 per cent for the pulp. It decreases with age, the loss being greatest during the first year of life. At 3 years of age, the water content of the ring is 70 per cent; that of the pulp, 76 to 78 per cent. The water content of the annulus remains practically constant at from 68 to 70 per cent from the third year on, whereas that of the pulp continues to decrease with age, falling to 70 per cent in the ninth decade. Disks that appeared swollen and abnormally moist had essentially the same water content as normal disks of the same age period. Disks that appeared abnormally dry or brittle or fissured had a decreased water content.

O. T. SCHULTZ.

CHEMICAL INVESTIGATIONS OF THE BLOOD AFTER DEATH. F. JACOBY, Virchows Arch. f. path. Anat. **274**:392, 1929.

The thrombin content after death is much lower than during life; it decreases rapidly; after twenty-four hours very little thrombin is left. Thus, late formation of postmortem thrombi is improbable. The results speak in favor of Ribbert's theory of agonal thrombosis. There are no basic morphologic differences between intravital thrombi and postmortem clots. The nonprotein nitrogen in the blood of the cadaver generaly is high; it increases slowly. The p_H was found to be about 7.11. High figures for nonprotein nitrogen were obtained in blood with an unusually strong acid reaction. The calcium figures do not differ from those found in the living subject. Twenty-six bodies were examined.

ALFRED PLAUT.

Microbiology and Parasitology

FETAL BACTEREMIA: A CONTRIBUTION TO THE MECHANISM OF INTRA-UTERINE INFECTION AND TO THE PATHOGENESIS OF PLACENTITIS. ALFRED J. KOBAK, Am. J. Obst. & Gynec. **19**:299, 1930.

The occasional presence of streptococci and other organisms in the blood from the umbilical cord, sent to the laboratory for use in mediums, prompted an investigation on a large scale to determine in what manner the fetus becomes infected

before or during labor. Thus 374 consecutive fetal blood cultures, aseptically drawn from the umbilical cord in the third stage of labor, were studied. Positive cultures were found in thirty-four cases, or about 9 per cent. In most instances these cases were associated with a prolonged rupture of the bag of waters. The organisms were found to be the type that usually frequents the vaginal canal in late pregnancies. Thus it is believed that they find their way into the amniotic fluid from which they get into the fetal circulation. The placentas were studied in all cases in which three cultures were positive, and also in any cases that had membranes unduly long ruptured and in which there was suspicion of utrapartum maternal infection. This study showed that the inflammatory reactions of the placenta is most often due to organisms in the amniotic waters. The organisms most likely break through the superficially placed chorionic blood vessels and enter the fetal circulation. In most instances this was only a transient bacteremia with no clinical significance. In a few instances of difficult birth, with a traumatism of the child from obstetrical procedures, severe and even fatal infection occurred. Four of the infants who died had the same bacteria in the heart blood as in the blood of the cord. Maternal infection also may take place in difficult labor.

A. J. KOBAK.

EXPERIMENTAL TUBERCULOUS MENINGITIS IN RABBITS. WILLARD B. SOPER and MORRIS DWORSKI, Am. Rev. Tuberc. **21**:209, 1930.

The previous observation that the protective action of an already existing infection is manifested in the meninges of the rabbit is confirmed. Two rabbits vaccinated with living human tubercle bacilli successfully overcame a small intrameningeal dose of virulent bovine bacilli fatal to controls. Rabbits subcutaneously vaccinated once with heat-killed tubercle bacilli showed a pronounced degree of protection against virulent bovine bacilli injected intrameningeally. This protection was less than that conferred by living bacilli. The white cell count of the cerebrospinal fluid following meningeal superinfection with small doses of tubercle bacilli was strikingly low in comparison with counts after similar infection with large doses. Differences in the immediate white cell reaction to intrameningeal infection on the part of vaccinated as compared to unvaccinated animals were negligble when the small dose of 200 bovine bacilli was employed.

H. J. CORPER.

AN ATTEMPT TO GROW TUBERCLE BACILLI IN GROSS TISSUES. H. J. CORPER, Am. Rev. Tuberc. **21**:252, 1930.

These studies on the growth of tubercle bacilli in normal and pathologic tissues have a practical bearing in that they offer an explanation for the inability of tubercle bacilli to grow directly on tuberculous tissues and excretions in vitro at incubator temperature; they indicate the futility of trying to increase the number of bacilli by this means for diagnostic purposes without overcoming the fundamental obstacles to such an increase in numbers, and they point out certain important precautions to be observed in the application of culture methods for diagnostic purposes. In the sulphuric acid-crystal violet-potato cylinder method previously recommended for diagnostic purposes, the thorough grinding or breaking up of the tissues or pathologic material was more or less empirically emphasized, as was a light well distributed planting over a number of culture tubes, which serves to bring the bacilli into intimate contact with the potato medium. At incubator temperature, the acid-treated tissues develop toxic autolytic products that destroy the tubercle bacilli, and intimate contact with the potato inhibits the formation of these toxic products in sputum, tissues, etc. This study also throws light on some of the apparent discrepancies between the in vivo and the in vitro growth of tubercle bacilli and stresses the importance of quantitative consideration in evaluating growth conditions in the body. Any attempt to study in vivo condi-

tions in tuberculosis by in vitro methods must take into consideration the possibility of the formation of toxic autolytic products for tubercle bacilli by the tissues under the conditions of the experiment, and, if possible, must take measures to obviate their formation or overcome their action by appropriate neutralizing or counteracting procedures.

H. J. CORPER.

THE REACTIONS OF THE TISSUES TO THE LIPOID FRACTIONS OF THE TUBERCLE BACILLUS STRAIN H37. FLORENCE R. SABIN, C. A. DOAN and C. E. FORKNER, Am. Rev. Tuberc. **21**:290, 1930.

The tissue reactions to five lipoid fractions from the tubercle bacillus are described. All of the lipoid substances were found to give a marked proliferative reaction in the connective tissues, which reaction was in part specific and in part nonspecific. The reaction may belong to the so-called foreign body type.

H. J. CORPER.

ARACHNIDISM. J. B. ELLIS, Ann. Int. Med. **3**:924, 1930.

In three of five cases of arachnidism the offending spider was caught and identified as *Latrodectus mactans,* which is thought to be the only poisonous spider in the United States. The symptomatology was practically identical in all of the cases: burning pain at the site of the bite, followed in approximately thirty minutes by severe backache, headache, pains in the abdomen and legs, profuse perspiration, extreme restlessness with rapid and difficult breathing. The symptoms gradually receded but did not disappear for several days. There were no deaths. The fact that one patient, who was bitten a second time two weeks after the first bite, developed a much milder illness following the second bite caused Ellis to assume that the patient developed some immunity as the result of the primary inoculation.

WALTER M. SIMPSON.

POSTVACCINAL (COWPOX) ENCEPHALITIS. GEORGE B. HASSIN and J. C. GEIGER, Arch. Neurol. & Psychiat. **23**:481, 1930.

In a case observed in January, 1926, a white boy, aged 7, with a condition diagnosed as tetanus, had been vaccinated against smallpox two weeks previous to admission to the hospital. Twelve days after the vaccination he began to have severe frontal headaches, soon followed by convulsions and lockjaw. The clinical picture was that of a typical tetanus; the patient was treated with tetanus antitoxin intramuscularly and intravenously; the condition grew worse; the temperature rose to 107.7 F.; a blood count showed 26,000 white cells per cubic millimeter, and the spinal puncture yielded a normal spinal fluid. Respiratory difficulties set in, and the patient died twenty hours after admission. Histologic studies revealed hyperemia of the blood vessels, mild infiltration of the perivascular spaces of the larger blood vessels mainly with glia cells which formed a much denser infiltration outside the adventitia, the so-called extra-adventitial infiltration. The capillaries showed no infiltrations. The infiltrated areas sometimes coalesced, forming extensive islands. The extra-adventitial areas exhibited no axons or myelin; the English authors named them areas of demyelination. Outside these the nerve substance was preserved, but the microglia was changed throughout; it was swollen and hypertrophied, the processes were tumefied, shortened and reduced in number and the nuclei were pyknotic and hypertrophied. The subarachnoid space was distended and contained fibroblasts, lymphocytes, polyblasts and macrophages. The ganglion cells were practically normal. The changes were similar to those described by others but were unique in taking place within twenty-three hours after the onset. The clinical picture of postvaccinal encephalitis may vary but the anatomic picture is the same; it differs from other forms such as epidemic encephalitis. From the histologic studies of the case and analysis of the views

as to the probable cause of the postvaccinal encephalitis, the authors come to the conclusion that it is not of infectious but of toxic origin, and that some toxin occasionally too virulent is contained within the vaccine lymph and invades the brain.

GEORGE B. HASSIN.

COCCIDIOIDAL GRANULOMA OF THE SPINAL CORD. CARL W. RAND, Arch. Neurol. & Psychiat. **23**:502, 1930.

Coccidioidal granuloma much resembles chronic tuberculosis. In California 143 cases have been reported to the State Board of Health against 98 cases reported in the literature. In Rand's cases the process involved the spinal cord. In the first case, that of a Mexican woman, aged 31, recurring pain of five years' duration was followed by weakness and spastic paralysis of the lower extremities with anesthesia up to the ninth dorsal segment of the spinal cord, exaggerated tendon reflexes, double Babinski sign and urinary incontinence. Spinal puncture showed a partial block. A coccidioidal granuloma, extradural, was found on operation at the level of the sixth vertebra. The patient recovered completely from the paraplegia, and there was no recurrence eight months later. Histologically, the growth resembled tuberculous granulation tissue, and *Coccidioides immitis* was present, with numerous giant cells of the Langhans type. In case 2, a man, aged 38, presented symptoms of tuberculous meningitis and infectious arthritis for about a year. Several infected teeth, the appendix and the gallbladder were removed. Shortly before death a quadraplegia developed which necropsy showed was due to a coccidioidal granuloma. This was subdural and surrounded the cervical region of the spinal cord like a cuff, especially at the level of the third and fourth segments. No apparent involvement of the cord itself was present but the pia was involved around the cervical cord, inferior surface of the cerebellum, pons and the Sylvian fissures.

GEORGE B. HASSIN.

HODGKIN'S DISEASE IN A CHILD. ELISE S. L'ESPERANCE, J. Immunol. **18**: 127, 1930.

Chicken inoculations of Hodgkin's material again resulted in typical avian tuberculosis, and reinoculation from this into other chickens caused a more extensive tuberculosis with marked involvement of bones. Cultures of material from a reinoculated chicken gave a pure growth of tubercle bacilli, culturally of avian type. Treated guinea-pigs inoculated with the original material developed extensive lymphatic tuberculosis and cultures on egg mediums showed many of the characteristics of a growth of avian tubercle bacilli. Subcutaneous inoculation of a rabbit with the original material caused no infection, as frequently happens with pure culture of avian tubercle bacilli.

AUTHOR'S SUMMARY.

A CASE OF PEL EBSTEIN'S SYNDROME OF TUBERCULOUS ORIGIN. ELISE S. L'ESPERANCE, J. Immunol. **18**:133, 1930.

The observations in the present case are of value from two angles: First, as offering evidence of the avian tuberculous nature of a condition which presents a histologic relationship to typical Hodgkin's disease, and secondly in indicating that in man as well as in lower animals, especially birds, avian infection may be exhibited in various pathologic lesions.

AUTHOR'S SUMMARY.

EXPERIMENTAL TYPHUS FEVER. H. A. REIMANN, J. Immunol. **18**:153; H. A. REIMANN AND C. J. WU, ibid. **18**:159, 1930.

The administration of india ink, sodium chaulmoograte, trypan blue and collargol before the inoculation of typhus virus in guinea-pigs usually prolongs the incubation time and shortens or diminishes the febrile reaction of typhus fever. The probable explanation of the results is discussed. Typhus fever in guinea-

pigs, rabbits and monkeys vaccinated with typhoid bacilli had no influence on the Widal reaction in these animals. Typhus fever had no influence on pneumococcus agglutinins or immunity in vaccinated or normal guinea-pigs.

AUTHORS' SUMMARY.

COWS INFECTED WITH STREPTOCOCCUS EPIDEMICUS (DAVIS). W. D. FROST, R. C. THOMAS, MILDRED GUMM and F. B. HADLEY, J. Infect. Dis. **46**:240, 1930.

Seventeen cows are reported in this paper which were shedding in their milk *Streptococcus epidemicus* Davis. Two of them were associated with an epidemic of septic sore throat. The other fifteen cows were giving milk which was mixed with a considerable quantity of other milk and used as food. Eight of these cows were found, during the course of four years, in certified herds of approximately 1,200 cows, which have been regularly tested at monthly intervals. The other seven were accidentally discovered in small herds. Our work would indicate that cows infected with *Streptococcus epidemicus* are rather generally and widely distributed, and that this streptococcus undoubtedly occurs quite generally and frequently in milk used for direct consumption, as well as that which is used for cheese and butter making without producing disease. The infection of cattle with this human type of streptococcus apparently begins as a mild disease, which may become very severe or apparently continue a mild course. There is a tendency for the infected portions of the udder to lose their milk secreting function. In the group of mild cases to which most of our cows belong, there is little or no change from the normal in either the udder or the milk, although *Streptococcus epidemicus* may be shed in large numbers. Of the thirteen cows in which the extent of the infection was determined, seven cows, 53 per cent, were infected in only one quarter, four cows, 31 per cent, were infected in two quarters, and two cows, 16 per cent, were infected in three quarters, although the infection in the different quarters did not always occur simultaneously. The strains of *Streptococcus epidemicus* are apparently all virulent and are identical with those strains isolated from epidemics from either man or cow.

AUTHORS' SUMMARY.

DISSOCIATION OF ORGANISM RESEMBLING BACILLUS VULGATUS. JOEL G. WAHLIN, J. Infect. Dis. **46**:253, 1930.

An organism resembling *B. vulgatus* morphologically and culturally has been studied. This organism undergoes spontaneous dissociation. The tendency to dissociate is not readily destroyed and is transmitted in the spore. Two variant types have been isolated which differ morphologically and culturally but not biochemically, so far as demonstrated.

AUTHOR'S SUMMARY.

ENDEMIC TYPHUS OF THE SOUTHEASTERN UNITED STATES (THE REACTION OF THE WHITE RAT). KENNETH F. MAXCY, Pub. Health Rep. **44**:1935, 1929.

The observations are interpreted, therefore, as indicating that the temperature rise which occurred in rats from three to six days after intraperitoneal injection of tissues containing the Wilmington virus, were due, at least in part, to the virus itself. Subsequent to this time, and quite regularly up to the thirteenth day, although the animal was afebrile and gave no outward evidence of infection, the virus was present and widely distributed in his body. It was demonstrated to be still present in the brain as late as the twentieth day after inoculation. The fever curve in rats, therefore, does not afford an indication of the course of the infection such as is usually the case in guinea-pigs and monkeys. The infection in the rat was, except for a brief period at the time of onset, afebrile and inapparent.

During this same brief febrile period at the beginning of the infection, it was found that the cells lining the tunica vaginalis were being extensively invaded

with the minute, Rickettsia-like micro-organisms which have been demonstrated to be associated with the virus. These were at first almost entirely intracellular and apparently multiplying rapidly. After a day or two, however, they were largely extracellular. Thereafter, they disappeared entirely from this location.

It seems not unlikely that the febrile reaction may have been in part associated with this rapid multiplication of the virus in the tunica. After this local reaction had subsided and the virus had become generally distributed in the various tissues, the fever disappeared and the infection ran an inapparent course.

These studies have shown that the white rat is a susceptible host to the Wilmington strain of typhus from the southeastern United States, and affords a particularly favorable species in which to study the Rickettsia-like micro-organisms.

AUTHOR'S SUMMARY.

VIRUS III IN TISSUE CULTURES. C. H. ANDREWS, Brit. J. Exper. Path. **10**: 273, 1929.

Virus III has been carried on in twenty-three serial in vitro cultures of rabbit testis in rabbit serum or plasma; it appears to have multiplied in vitro at least 8 by 10^{27} times. The conditions under which inclusion bodies form in such cultures have been further studied. Virus III will not survive nor form inclusions in cultures of immune testis in immune serum or plasma. Virus III will not survive nor form inclusions in cultures of normal testis in immune serum or plasma, provided that the immune fluid is added to the tissue in the culture before the virus. Virus III will survive and form inclusions in cultures of immune testis in normal serum or plasma, particularly if the immune tissues are subjected to a brief preliminary soaking in Tyrode's solution. If virus and tissue are incubated together for a short time before immune serum or plasma is added to culture, the virus can infect the cells and form inclusions, despite the presence of antibody in the fluid bathing the cell. Experiments are described which seem to indicate that Virus III can infect cells within ten minutes at 37 C., but that it cannot do so even after five hours at 6 or —2.5 C.

AUTHOR'S SUMMARY.

EXPERIMENTAL BRUCELLA ABORTUS INFECTION IN MAN. P. MORALES OTERO, Porto Rico Rev. Pub. Health & Trop. Med. **5**:144, 1929.

Of five normal persons fed *Brucella* cultures in milk, two developed fever-like undulant fever. In these two cases the cultures introduced were of the porcine variety; the blood yielded cultures of this strain on the fifth and seventh day of disease respectively.

THE ETIOLOGY OF SEROUS EFFUSION IN ARTIFICIAL PNEUMOTHORAX. W. STOBIE, Tubercle **11**:253, 1930.

From the literature serous effusions in artificial pneumothorax may be caused by the local anesthetic, the cold air, too rapid filling, irritation of the gas, too much gas, pressure on the pulmonary vessels at the root of the lung, intercurrent diseases, the introduction of minute portions of the tissues through which the needle has passed, overexertion, menstruation, injury of the visceral pleura, stage of the disease, separation of adhesions and so on, while on the opposite side it is generally agreed that age, sex, type of disease and resistance have little or nothing to do with the onset of an effusion. Seasonal incidence has little or no effect on the number of cases. There is one common factor, viz., the separation of the pleural surfaces by the inflowing gas, and the one outstanding feature in those in which fluid developed was the presence of adhesions, generally in the upper part of the lung. Extension of the disease in the other lung sooner or later results in hematogenous or other methods of spread and greater likeliness to effusion.

H. J. CORPER.

GLANDERS OF THE LUNGS SIMULATING PULMONARY TUBERCULOSIS. E. H. A. PASK, Tubercle **11**:257, 1930.

Glanders of the lungs is a rare disease and is usually acute and rapidly fatal, being part of a general septicemia. The case reported was of a more chronic type, closely simulating pulmonary tuberculosis with death six months after the onset of the symptoms in the chest. The patient was a man, aged 35. The sputum was negative for tubercle bacilli, but glanders developed in the guinea-pigs.

H. J. CORPER.

A CASE OF HERPETIC URETHRITIS. PAUL DURAND and R. DELEUIL, Arch. Inst. Pasteur de Tunis **19**:36, 1930.

Urethritis was noted in a young man four or five days following several days of chills and fever, during which herpetic vesicles had appeared on the lips. A small ulcer appeared, not preceded by any noted vesicular stage, which was accompanied by a tingling sensation, exaggerated at the time of micturition. Bacteriologic examination gave entirely negative results. Following a strong and painful pressure on the urethra, a large drop of grayish, viscous fluid was secured, containing numerous polymorphonuclear and endothelial cells, but no organisms. Inoculation by scarification of the cornea of a rabbit was followed progressively by inflammation of the iris, fever, intense keratitis and chemosis, paraplegia and finally a rapid drop in temperature to 30 C. (86 F.) and death on the twelfth day. Cultures were negative. The brain was preserved in 50 per cent glycerin. Subsequent serial passages through rabbits by intracerebral inoculation of glycerin brain suspensions produced the typical syndrome of encephalitis apparently due to a very potent strain of virus.

M. S. MARSHALL.

THE LOCAL NEUTRALIZATION OF RABIES VIRUS. CLAUDIO FERMI, Zentralbl. f. Bakteriol. **112**:73, 1929.

The dissemination of rabies virus subsequent to its subcutaneous injection can be prevented in rats if solutions of 1:10,000 mercuric chloride, 1:1,000 silver nitrate, 2 per cent phenol or 1:200 methylene blue (methylthionine chloride, U. S. P.) are injected immediately around the point of injection. After fifteen minutes, however, such injections are of no avail. The absorption of the virus through the nasal mucosa and the rectum is so rapid that in fifteen minutes no method will prevent rabies. Amputation of the tail, even five hours after inoculation, was successful, as was also local passive hyperemia by means of elastic binders, which saved all of the animals tested, even when employed four hours after infection.

PAUL R. CANNON.

EXPERIMENTAL MEASLES IN RABBITS. P. BELIKOFF, P. P. DWIJKOFF AND E. TRUSCHINA, Zentralbl. f. Bakteriol. **112**:78, 1929.

The authors injected rabbits with blood and filtrates of the pharyngeal mucosa from patients ill with measles, and in some instances fever, slight leukopenia and mucosal and skin reactions appeared. Similar results were also observed subsequent to the injection of a pure culture of a diplococcus recovered from patients with measles. Inflammation was found around the blood vessels with proliferation of the adventitial elements, frequently mixed with polymorphonuclear leukocytes. These changes were most marked in the skin; to a lesser degree in the larynx and trachea with, at times, hemorrhages in the mucosa. These changes were not observed following the injection of blood and mucosal filtrates from patients free from measles. Several photographs illustrate the changes.

PAUL R. CANNON.

THE NATURE OF THE ANTIVIRUS OF BESREDKA. H. ALDERSHOFF, Zentralbl. f. Bakteriol. **112**:273, 1929.

As a result of studies in vitro on Besredka's "antivirus," Aldershoff concludes that this is not specific and is not even dependent on growth of the virus itself, as the same effect can be demonstrated after several filtrations of uninoculated broth through Chamberland and E K filters. The degree of inhibition varies directly with the number of times the broth has been filtered. This inhibiting substance is thermostable and is not the result of the removal of colloidal substances, fat, sugar or salts. The author thinks it probable that repeated filtrations lead to a colloidal-chemical change in part of the protein in the broth so that it is not available for bacterial growth and even inhibits growth.

PAUL R. CANNON.

Immunology

TUBERCULO-ALLERGY IN SKIN TRANSPLANTS. A. H. W. CAULFEILD, M. H. BROWN and WILLIAM MAGNER, Am. Rev. Tuberc. **21**:127, 1930.

The results obtained indicate that in each experiment marked differences are manifest in the reactions that take place in the immune and normal grafts to tubercle bacilli and to a less extent to tuberculin, and that the usual reaction of the immune graft approximates that which takes place in the immune skin rather than in the normal skin and is demonstrable in three ways: 1. Following injection, tubercle bacilli are immobilized in the immune graft and their extension throughout the lymphatic system is delayed in a manner comparable to what takes place in the immune animal. 2. Following the injection of bacilli into immune grafts the usual reaction is relatively rapid and intense and more closely resembles that induced in the skin of the immune animal than that in the normal skin or graft. 3. Evidence of persisting sensitization of the immune graft to tuberculin was found in that gross swelling and microscopic infiltration were present. The difference between reactions so obtained in the immune and normal grafts has not been as constant or as marked in degree as that which occurred with the use of tubercle bacilli.

H. J. CORPER.

THE INHIBITIVE REACTION OF CAULFEILD. A. C. NORWICH, M. F. MACLENNAN and M. F. BASSINGTHWAIGHTE, Am. Rev. Tuberc. **21**:142, 1930.

The inhibitive reaction of tuberculosis (*J. M. Research* **24**:100, 1911, and *Am. Rev. Tuberc.* **11**:508, 1925) is specific for tuberculous serum and appears more frequently in the tuberculous than in the supposedly nontuberculous. The reaction is a valuable aid, occasionally in diagnosis but more frequently in prognosis. The test is a type of complement fixation in which the amount of hemolysis is used as an index of the degree of reaction, that is, the amount of hemolysis as indicative of the amount of "inhibitin" present in the serum. (The original technic is given in *Proc. Roy. Soc.*, Sec. B., 1911, vol. 84.) The test brings together a lipoidal tuberculo-antigen, the inactivated serum to be tested, complement, and, after an interval, sensitized corpuscles. The anticomplementary strengths of the antigen used bar it from being regarded as a modification of the tuberculo-complement-fixation. The test is done by adding serum to three multiple dilutions of tuberculo-lipoidal antigen (accurately titrated as to anti-complementary strength), and the end-results show as degrees of hemolysis or no hemolysis. The hemolytic system is guinea-pig complement, sheep's corpuscles and antisheep rabbit serum for hemolysin. The serums to be tested are inactivated by immersion in a water-bath one-half hour at 56 C.

H. J. CORPER.

THE CHEMICAL COMPOSITION OF THE ACTIVE PRINCIPLE OF TUBERCULIN. FLORENCE B. SEIBERT, Am. Rev. Tuberc. **21**:370, 1930.

It is possible to produce antibodies to the proteins from acid-fast bacteria. Precipitins were produced in normal guinea-pigs and rabbits by immunizing them with small doses (about the same as of other proteins) of the proteins obtained from culture liquids of human, bovine and avian tubercle bacilli and the timothy bacillus. The precipitin test can serve as a reliable diagnostic method for tuberculosis in the guinea-pig, since no normal unusued guinea-pig serum contains precipitins for the tuberculin protein, and practically all tuberculous serums do contain them. The precipitin test is not an adequate test for diagnosing human tuberculosis; only six serums out of fifty-one from cases of active tuberculosis showed precipitins. By means of cross precipitation reactions it is possible to distinguish easily between the proteins from the human, bovine and avian tubercle bacilli and the timothy bacillus.

H. J. CORPER.

SENSITIZATION IN EXPERIMENTAL TUBERCULOSIS. RUBY M. BOHART, Am. Rev. Tuberc. **21**:383, 1930.

Tubercle bacillus filtrates, such as the tuberculins, and proteins derived from them do not cause sensitization in guinea-pigs when tested by the old tuberculin intracutaneous skin reaction. Killed tubercle bacilli are effective sensitizers under certain conditions. Light-killed tubercle bacilli were found to be less efficient than heat-killed bacilli, while bacilli killed by certain chemicals, such as carbol fuchsin or ether, were the most efficient.

H. J. CORPER.

THE IMMUNOLOGICAL SIGNIFICANCE OF COLOSTRUM. THEOBALD SMITH, J. Exper. Med. **51**:473, 1930.

The protective antibody content of normal cow serum is below that of colostrum of the same animal. The method used does not permit the titration of the actual amount of the antibody in serum. Quantities up to 2 cc. have no protective effect. The same limitations apply to the titration of milk owing to the introduction of large quantities of foreign protein into the peritoneal cavity of the guinea-pig. When cows were immunized and a serum of high titer obtained, the antibodies in the milk of such cows rose to within the range of the method of testing. The relation of the protective capacity of serum to that of milk was approximately $\frac{1}{120}$ and $\frac{1}{40}$ in the two animals. These figures do not differ much from those obtained by early investigators titrating the antitoxic content of serum and milk of animals undergoing immunization with diphtheria toxin. In the two experiments on calves, 2¼ and 18 days old, respectively, fed a highly protective serum, no increase in agglutinins or protective antibodies could be demonstrated. The postponement of colostrum to the twelfth and eighteenth hour, respectively, did not prevent normal growth.

AUTHOR'S SUMMARY.

THE IMMUNOLOGICAL SIGNIFICANCE OF COLOSTRUM. THEOBALD SMITH AND RALPH B. LITTLE, J. Exper. Med. **51**:483, 1930.

Under certain safeguards, such as isolation, calves from a large dairy herd have been raised by feeding normal and immune cow serum in place of colostrum. The losses were about one of ten in the later experiments. This outcome may probably be improved by the subcutaneous injection of serum during the first day. This loss may be no greater than that under ordinary conditions, since sporadic deaths among calves are not infrequent. However, no satisfactory statistics are available for comparison with results as given.

AUTHORS' SUMMARY.

MODE OF ACTION OF A VIRICIDAL SERUM. S. P. BEDSON, Brit. J. Exper. Path. **10**:364, 1929.

The experiments demonstrate that collodion particles are capable of absorbing either herpes virus or herpes antibody. It is further shown that there is an increased avidity for the virus possessed by the particles which have been sensitized with herpes antiserum. The antibody is not liberated when the sensitized particles are soaked in phosphate buffer or normal guinea-pig pad suspension. Hence, it is argued that its liberation in the presence of virus would mean a specific and powerful attraction of virus for antibody. Therefore, it is concluded that herpes virus and antibody unite in vitro.

J. N. PATTERSON.

IMMUNITY TO HAEMOLYTIC STREPTOCOCCI. RONALD HARE, Brit. J. Exper. Path. **10**:375, 1929.

Hemolytic streptococci from broth cultures near the logarithmic phase are better fitted to withstand the bactericidal power of normal human defibrinated blood than those from cultures in the phase of decline. This is probably due, in part, to the ability of streptococci from cultures in the logarithmic phase to multiply faster in the serum moiety of the blood than those from cultures in the phase of decline, and, in part, to the assumption by growing streptococci of some degree of resistance to phagocytosis and its disappearance when the cocci become senescent. The importance of this principle in experimental work on immunity and also in the epidemiology of streptococcal infections is commented on.

AUTHOR'S SUMMARY.

ELECTRIC CHARGE IN ITS RELATION TO COMPLEMENT FIXATION. H. C. BROWN and J. C. BROOM, Brit. J. Exper. Path. **10**:387, 1929.

Under normal conditions the various components of complement-fixation reactions all carry negative charges. The effect of electrolytes in suitable concentrations is to lower the negative charge of the antigen-antibody complex to a degree dependent on the valency of the cation and the concentration of the immune serum. Electrolytes with polyvalent anions inhibit hemolysis because they maintain the negative charge of the sensitized cells. We are of the opinion that the reduction of charge of the antigen-antibody complex is an essential preliminary in the process of complement-fixation.

AUTHORS' SUMMARY.

COMPLEMENT-FIXATION WITH FILTERABLE VIRUSES. S. P. BEDSON and J. O. W. BLAND, Brit. J. Exper. Path. **10**:393, 1929.

Specific complement-fixation with the viruses of vaccinia and herpes can be obtained with hyperimmune serums prepared in the guinea-pig. A prolonged period of fixation is necessary for the satisfactory demonstration of this reaction. Evidence has been obtained that bacterial contamination of the virus antigens plays no part in this reaction. Some evidence has been produced to show that zoster vesicle fluid gives specific fixation in the presence of zoster convalescent serums.

The evidence adduced is further proof that virus and antibody unite outside the animal body.

AUTHORS' SUMMARY.

THE ACTION OF CERTAIN DYES ON THE BACTERICIDAL ACTIVITY OF NORMAL SERUM AND ON HEMOLYTIC COMPLEMENT. J. GORDON, J. Path. & Bact. **33**: 47, 1930.

Congo red and similar dyes prevent the bactericidal and hemolytic activities of serum. This is not associated with destruction of complement or of immune body. Sensitization of red blood corpuscles takes place in the presence of congo red. The addition of magnesium sulphate increases the action of this dye. Congo red

inhibits bactericidal activity in small concentrations than those in which it inhibits hemolytic activity. Charcoal removes congo red from an inactive mixture of complement-containing serum and dye, restoring to its hemolytic activity.

AUTHOR'S SUMMARY.

THE SPECIFICITY OF ACTIVE IMMUNITY AGAINST SNAKE VENOMS. C. H. KELLAWAY, J. Path. & Bact. **33**:157, 1930.

The specificity of active immunity to snake venoms, like that of passive immunity, depends on two factors: the zoological relationship of the reptiles yielding the venoms, and the "toxic constitution" of the venoms themselves. In active immunity against snake venoms, specificity appears to be somewhat less strict than in passive protection with univalent serums; active protection against a single venom also provides protection, in some cases by no means inconsiderable, against the venoms of closely related species. Close species relationship between the reptile supplying the venom used for immunization and that whose venom is used for testing appears to be even more important in determining nonspecific protection than close similarity between the venoms in regard to their toxic behavior.

AUTHOR'S SUMMARY.

TISSUE-CULTURE IN THE STUDY OF IMMUNITY TO HERPES. C. H. ANDREWES, J. Path. & Bact. **33**:301, 1930.

Herpes virus will multiply in "tissue-cultures" of the testis of a rabbit in dilute rabbit serum; this virus has been carried on in twenty-three serial cultures. Even though cultivated in testis, it has not changed its neurotropic properties during the course of eighteen passages. Herpes virus will regularly form in "tissue cultures" inclusion bodies like those that it forms in the testis and other organs of a living rabbit. Herpes virus will not multiply, or form inclusions in "tissue cultures" in the presence of immune serum, provided that this is added to the culture before the virus, or together with it. Antibodies develop readily in rabbits infected with herpes. Hyperimmunization is not necessary for their demonstration. Herpes virus will grow and form inclusions in cultures of immune testis in normal serum. Herpes virus can infect normal tissues in the absence of imune serum within half an hour at 17.5 C. or 37 C.; it can then grow and form inclusions in spite of the subsequent addition of immune serum. It can also infect immune tissues very quickly (forty-five minutes at 37 C.). A strain of herpes passaged in rabbits for five years will infect cultures of guinea-pig tissues, apparently as readily as those of the rabbit. Cross-immunity experiments in tissue cultures show that herpes and virus III are immunologically distinct.

AUTHOR'S SUMMARY.

A CRITICAL REVIEW OF THE SCHICK TEST AND ITS APPLICATION. S. F. DUDLEY, Quart. J. Med. **22**:321, 1929.

This article is a scholarly and concise review of the Schick test, giving a historical outline, technic and interpretation. It is divided into twenty-six small chapters, and an extensive bibliography is attached.

N. ENZER.

THE BLOOD GROUPS IN THE DIFFERENT RACES IN TUNIS. LOUIS CAILLON and CAMILLE DISDIER, Arch. Inst. Pasteur de Tunis **19**:41, 1930.

A significant difference in the distribution of different blood groups among the inhibitants of Tunis is noted which "confirms what is already known regarding the history of the mixture of races" living in this region. A succeeding paper (p. 50) by the same authors considers more in detail the blood groups of the Berbers, a more strictly localized group.

EXPERIENCES WITH DIPHTHERIA ANATOXIN. MARCELLE NICOLLE, Arch. Inst. Pasteur de Tunis **19**:55, 1930.

Over a period of eighteen months, 907 persons were given injections of diphtheria anatoxin or toxid, 789 of whom received the full three injections, 0.5, 1.0, and 1.5 cc., spaced respectively at three week and fifteen day intervals. The age group ranged from 1 to 37 years, the younger ages predominating. Following the first injection, low fevers were noted in approximately 1 per cent of the cases, lasting a maximum of three days. Reactions were more marked following the second injection, occurring in some 4 per cent of the persons, with higher temperatures. No reactions were noted after the third injection. Reactions in children under 5 years of age were not observed.

M. S. MARSHALL.

EXPERIMENTAL ALLERGIC ARTHRITIS. F. KLINGE, Beitr. z. path. Anat. u. z. allg. Path. **83**:185, 1929.

In previous work of the author, the injection of horse serum into the joint cavity of rabbits sensitized by the subcutaneous injection of horse serum led to acute, purulent and destructive inflammation of the joint. He believed that by modifications of the experimental procedure it should be possible to bring about changes in the joints comparable with those of rheumatic polyarthritis. The present report relates to such experiments conducted during the course of two years. The procedures were varied in a number of ways, and the resulting process in the joint tissues was studied microscopically. The rabbit was the animal used. A single injection of from 1 to 2 cc. of sterile horse serum into the knee joint of the normal rabbit caused only slight hyperemia of the synovial membrane, in which a few leukocytes were sometimes found microscopically. The injection of heterologous serum into the joints of animals sensitized to horse serum also caused little reaction, but somewhat more than that with the previous procedure. If the animals were sensitized during the course of four weeks by repeated subcutaneous injections and then received a single injection of horse serum into the joint, there resulted the acute purulent destructive arthritis noted in the earlier series of experiments. In a fourth series, the animals received two sensitizing subcutaneous injections of horse serum separated by a three day interval. Four weeks later, each animal received into the joint the first of a series of five injections distributed over a period of about four months. There resulted a productive monocytic and histiocytic inflammation of the synovia, with subendothelial hyaline necrosis that led to ulceration. Areas of waxy necrosis and focal areas composed of large mononuclear cells were present in the skeletal muscles. Focal subendothelial necroses occurred in the walls of the arteries and veins. The heart valves were thickened by edematous young connective tissue. The heart muscle contained periarterial nodules of large mononuclear cells and larger areas of muscle cell necrosis surrounded by cellular infiltration. Sensitization by five injections of horse serum, followed by two injections into the joint, led to a similar reaction in the joint and to necrosis and the formation of nodules or large cells in the periarticular muscles. Sensitization with a single dose of 2 cc. of serum, followed by nine intra-articular injections of 0.25 cc. serum in the course of five months led to destructive joint lesions, the progress of which could be followed roentgenologically for long periods after the last injection. Of two animals that received repeated small subcutaneous injections of serum during the course of six months, one developed a polyarthritis that involved most of the large and many of the small joints. Klinge concludes that by the proper gradation of sensitizing and intra-articular injections of horse serum it is possible to cause changes in the joints, perivascular tissues and muscle that have great similarity to those of human rheumatic arthritis.

O. T. SCHULTZ.

THE NATURE OF IMMUNITY IN RELAPSING FEVER. W. K. BELEZKI and R. M. UMANSKAJA, Virchows Arch. f. path. Anat. **272**:305, 1929.

In four cases of relapsing fever in human beings the inner organs were examined with a special silver method. In all organs many more spirochetes, in more or less disintegrated condition, were found in the blood than within cells. Phagocytosis played no important rôle. Granulocytes did not contain spirochetes; as far as there was phagocytosis it was done by histiocytes. The organs that have many reticulo-endothelial cells contained the largest number of spirochetes (spleen, suprarenal glands, liver). In the central nervous system and its vessels nearly all the spirochetes were unaltered. Phagocytosis was by neuroglia cells and by Hortega cells. These results correspond to those in experimental relapsing fever in mice. But in the mouse phagocytosis is still more scanty, and the spirochetes are more localized in the tissue than in the vessels.

ALFRED PLAUT.

THE HEREDITARY TRANSMISSION OF ACQUIRED IMMUNITY THROUGH THE GERM PLASM. OTTO HERRMANN, Zentralbl. f. Bakteriol. (Abt. 1) **112**:460, 1929.

The author finds that the acquired immunity in rabbits to rabies virus is transmitted to the young and may persist for six to eight months. This immunity has been transmitted by females even when the pregnancy began from six to nine months after the termination of the immunization. The immunity has also been transmitted by the males as long as from one to seven and one-half months after the termination of the immunization. When both parents are immune a greater proportion of the young are immune. Apparently the immunity may even be transmitted to the third generation, although more animals must be studied to confirm this point.

PAUL R. CANNON.

THE KAHN REACTION IN EXPERIMENTAL SYPHILIS IN RABBITS. T. SAITO, Ztschr. f. Hyg. u. Infektionskr. **110**:603, 1929.

Saito reports that in normal rabbits the Kahn reaction with dilute serum is always negative while in animals infected with syphilis the result is distinctly positive.

W. OPHÜLS.

HEMOGLOBINURIA IN MALARIA. M. K. EBERT, Ztschr. f. Immunitätsforsch. u. exper. Therap. **65**:161, 1930.

The degree of hemolysis has no relation to any of the blood groups.

PHYSICOCHEMICAL PROPERTIES OF ISO-AGGLUTININS AND THE MECHANISM OF ISOHEMAGGLUTINATION. VERA SCHRÖDER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **65**:81, 1930.

This is an effort to explain isohemagglutination on the basis of electrochemical and colloidochemical processes.

THE FORMATION OF ANTIBODIES IN RABBITS PREVIOUSLY INFLUENCED BY THE INJECTION OF SERUM GLOBIN. P. VON GARA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **65**:176, 1930.

Rabbits, in which globulin fractions of immune serum have been injected about five or six weeks before the introduction of antigen—typhoid bacilli, blood corpuscles and foreign protein—responded with a much more liberal production of free specific antibodies than rabbits not subjected to any preliminary treatment.

ORAL TYPHOID AND PARATYPHOID INOCULATION. O. OTTOLENGHI and G. BROTZU, Ztschr. f. Immunitätsforsch. u. exper. Therap. **65**:195, 1930.

The value of oral antityphoid inoculation in human beings is not established, but the method is not without some action. Rabbits are immunized easily by mouth

against fatal typhoid and paratyphoid infections; the immunity reaches its height in about two weeks at the same time as agglutinins and other antibodies in the blood are at the climax. Claims to the contrary notwithstanding, oral inoculation calls forth the new formation of antibodies—the organism as a whole reacts.

INTRACUTANEOUS TEST FOR MALARIA. O. HERRMANN and M. LIFSCHITZ, Ztschr. f. Immunitätsforsch. u. exper. Therap. **65**:240, 1930.

Using an antigen, extracts of clotted blood from malarial patients, cutaneous reactions were obtained in most of the malarial patients that were tested, but not in healthy persons or patients suffering from other diseases than malaria.

QUANTITATIVE STUDIES OF HUMAN ISO-AGGLUTININS. K. KETTEL and O. THOMSEN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **65**:245, 1930.

In groups O and B the curves of the agglutinins for Groups A are practically identical. In group O the agglutinin for group A has a higher titer than the agglutinin for group B. Other details must be sought in the original article.

INFLUENCE OF SPLENECTOMY IN TRYPANSOMIASIS IN DOGS. O. NIESCHULZ and F. K. WAWO-ROENTOE, Ztschr. f. Immunitätsforsch. u. exper. Therap. **65**: 312, 1930.

Splenectomy was without effect on the disease in dogs infected with *Schizotrypanum cruzi*, but in dogs infected with *Trypansoma gambiense*, splenectomy deprived the animal of its main protection against the infection.

COMPLEMENT IN RELATION TO THE RETICULO-ENDOTHELIAL SYSTEM. J. LANDSBERGER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **65**:385, 1930.

No relation could be established between the content of complement in the serum and the functional variations on part of the reticulo-endothelial system.

GROUP SPECIFIC ANTIGENS IN HUMAN ORGANS. I. L. KRITSCHEWSKI and R. E. MESSIK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **65**:405, 1930.

Alcoholic extracts of the brain of persons belonging to groups II and III contain group antigens A and B. These antigens are not the same as the Forssman antigen and their lipoid nature is not established.

ISOHEMOPSONINS. P. L. RUBINSTEIN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **65**:431, 1930.

Human serum contains in addition to iso-agglutinin also isohemopsonin (isohemotropin).

Tumors

PRIMARY CARCINOMA OF VAGINA FOLLOWING BALDWIN RECONSTRUCTION OPERATION FOR CONGENITAL ABSENCE OF VAGINA. R. N. RITCHIE, Am. J. Obst. & Gynec. **18**:794, 1929.

A woman, aged 26, who complained of pelvic pain and vaginal discharge was found to have an adenocarcinoma of the posterior vaginal wall which was in communication with the rectum through a small incision. The external genitalia were normal, but investigation revealed that at the age of 13 years the patient had had an artificial vagina made from a loop of bowel due to congenital absence of a vagina.

GEORGE RUKSTINAT.

SANGUINEOUS DISCHARGE FROM THE NIPPLE AND ITS RELATION TO CARCINOMA. F. E. ADAIR, Ann. Surg. **91**:197, 1930.

Forty-seven and two-tenths per cent of 108 cases having a sanguineous discharge from the nipple were found to be malignant, which concurs with the previous reports of Miller, Judd and Lewis. It is emphasized that microscopic examination is essential in concluding that the discharge is really blood. Usually intracanalicular papilloma results in a serous or blood-stained discharge, whereas carcinoma causes the appearance of frank blood, and chronic mastitis produces a chocolate, green or yellow discharge. In this group it was noted that papillary cysto-adenoma was frequently a precursor of adenocarcinoma.

RICHARD A. LIFVENDAHL.

MALIGNANT TUMORS OF THE NAIL BED. R. H. JAFFÉ, Surg. Gynec. & Obst. **50**:847, 1930.

In persistent ulcerative lesions of the nail bed, melanoblastoma and squamous cell carcinoma must be considered. Although the lesions are rare, the author reports the pigmented tumor on the great toe of a woman, aged 69 years, who presented an oval ulcer with sharp, indented, and occasionally undermined edges and a gray purple granulated base extending down close to the bone; near the posterior border there was a thin brown line due to intracellular accumulations of melanotic pigment. Squamous cell carcinoma is exemplified by a second case in which a raised ulcer with a firm, dry, scaling, and waxy-appearing floor replaced the nail and extended over the anterior upper part of the toe. Benign tumors do not break through the nail.

RICHARD A. LIFVENDAHL.

OAT-CELL TUMORS OF MEDIASTINAL GLANDS. J. B. DUGUID AND A. M. KENNEDY, J. Path. & Bact. **33**:93, 1930.

Barnard's suggestion, that the "oat-cell sarcoma" of the posterior mediastinum is a medullary carcinoma of the bronchus, is recalled. A tumor of the thymus and a tumor of the mediastinal lymph glands, both showing oat cell features, are reported. The conclusion is that oat cell forms in a mediastinal tumor must not always be interpreted as indications of a bronchial origin.

AUTHORS' SUMMARY.

PRIMARY MALIGNANT INTRATHORACIC TUMORS. JAMES MAXWELL, J. Path. & Bact. **33**:233, 1930.

A series of 239 cases of primary malignant intrathoracic tumors is discussed, and the histologic appearances are recorded in 135 of these cases. Primary bronchial carcinoma was found to occur in 184 cases. The chief morbid anatomic observations are described, and the microscopic observations in 111 cases are discussed; reasons are given for accepting all of these cases as carcinomas in two main groups, an obvious columnar cell group with a tendency to squamous metaplasia and a small oval cell group which is slightly commoner. The oval celled carcinomas are discussed in detail, and reasons are given for the conclusion that they spring from the basal layer of the bronchial epithelium. It has not been shown that any of the tumors in this series arose directly in the epithelial lining of the pulmonary alveoli. The mediastinal tumors are shown to be a heterogeneous group, some being the result of infiltration or metastasis from a small primary bronchial focus, others being accepted as sarcomas arising in the mediastinal glands. No conclusive evidence could be found to show that any arose within the thymic remnants. Primary pleural tumors are shown to be a rare but well-defined group and are briefly discussed.

AUTHOR'S SUMMARY.

AN EMBRYONIC TUMOR OF THE LIVER CONTAINING STRIATED MUSCLE. H. L. SHEEHAN, J. Path. & Bact. **33**:251, 1930.

In a young girl the liver contained a number of papilliferous cysts lined by bile duct epithelium. The substance of the papillae consisted of undifferentiated cells. These cells in one cyst became malignant and formed a large tumor, destroying every other tissue except bile duct epithelium and showing a tendency to intravascular growth but not to metastasis outside the liver. They also differentiated into four types of more mature cells, including striated muscle. They are considered to be rest cells of mesoblast.

AUTHOR'S SUMMARY.

MULTIPLE MALIGNANT NEOPLASMS. JOHN W. ORR, J. Path. & Bact. **33**:283, 1930.

Three cases in which two independent carcinomas were present are described. A study has been made of the frequency of the occurrence of multiple malignant neoplasms. The view is expressed that there is no etiologic relationship between such tumors, and that they occur purely as the result of coincidence.

AUTHOR'S SUMMARY.

SPINAL METASTASES OF ASTROCYTOMA FIBRILLARE. DOROTHY S. RUSSELL and HUGH CAIRNS, J. Path. & Bact. **33**:383, 1930.

The case described here is one of astrocytoma fibrillare of the right optic thalamus. The tumor gave rise to no serious symptoms until four months before death, when hydrocephalus set in and advanced rapidly. This hydrocephalus was due to the obstruction of the aqueduct of Sylvius. The tumor was firm, and in its edge were numerous calcified areas which in life had revealed the outline of the tumor in x-ray films. On histologic examination, the tumor was found to be composed entirely of fibrillary astrocytes. It had invaded the subarachnoid space by way of the right pulvinar. Miliary metastatic nodules were found in the subarachnoid space over the superior medullary velum and in the subarachnoid space of the spinal cord. These metastases were entirely composed of fibrillary astrocytes, and thus presented the same degree of differentiation as did the primary tumor; they gave rise to no recognizable clinical symptoms.

AUTHORS' SUMMARY.

A TRANSPLANTABLE MELANOMA OF THE MOUSE. HAROLD E. HARDING and R. D. PASSEY, J. Path. & Bact. **33**:417, 1930.

This melanoma behaves like any other transplantable mouse tumor; it grows progressively on grafting into other mice, it recurs after an incomplete operation for removal, it is invasive and sometimes gives rise to metastases. A large proportion of the cells in the tumor are extraneous phagocytic cells full of melanin.

AUTHORS' SUMMARY.

CONGENITAL MALIGNANT TUMOR OF THE LIVER (PLACENTAL TRANSMISSION). F. P. WEBER, E. SCHWARZ and R. HELLENSCHMIED, München. med. Wchnschr. **77**:624, 1930.

A woman with a malignant melanoma was delivered by cesarean section at the thirty-eighth week of a seemingly healthy male child. The placenta contained many tumor nodules. The mother died three months later. The child had an enlarged nodular liver at 8 months of age and died at 11 months. There were found melanotic tumors in the liver and lymph nodes.

EDWIN F. HIRSCH.

On Heterogeneous Neoplastic Implantation. G. de Gaetani, Tumori **4**: 1, 1930.

The author has studied various factors influencing resistance and receptivity toward the subcutaneous and intracerebral inoculation of an adenocarcinoma of the mouse in rats by means of splenectomy, blocking of the reticulo-endothelial system, irradiation, and splenectomy plus injection of testicular extract. From the macroscopic, histologic and biologic results, as well as from the control of the lytic power of the serum, he concludes that the oncolytic power first exercises its injurious influence on the inoculated heterologous tumor, and that a decrease of oncolytic power favors the attachment of the tumor; in the second place, the unreceptivity of a different species, as an expression of a different biochemical condition of the host, comes into play and provokes arrest of growth, involution and necrosis of the heterologous tumor. The oncolytic power can be decreased by splenectomy, while it remains high in spite of irradiation in increasing doses and in spite of blocking of the reticulo-endothelial system.

W. Ophüls.

The Results of a Study of Hospital Statistics of Twenty-Five Years in Regard to the Age at Which Malignant Tumors Arise. A. Bonanno, Tumori **4**: 67, 1930.

From the study of 5,344 cases of malignant tumors observed from 1901 to 1925 at the Mauritian Hospital in Turin, it appears that the greatest frequency of occurrence is in the age period from 40 to 50. However, in persons under 30 years of age there were observed 342 cases of malignant tumors. In the last five year period there was observed, for women, a lowering of the level of age at which cancer is contracted. Important also is the recognition of the different distribution of malignant tumors of certain organs in regard to age.

Author's Summary.

Medicolegal Pathology

Fatal Emetine Poisoning, Due to Cumulative Action, in Amoebic Dysentery. Frank J. Leibly, Am. J. M. Sc. **179**:834, 1930.

Emetine is a protoplasmic poison acting on the host, as well as on the parasite, and there is no established course of treatment with this drug that can be accepted with impunity. The minimal lethal dose of emetine has not been satisfactorily determined for man. Conclusions drawn from laboratory animals are not applicable, owing to differences of species and of individual susceptibility. Death due to the cumulative action of emetine can occur without the advent of sufficiently severe symptoms to warn the physician before the minimal lethal dose has been passed. Cases of susceptibility to emetine cannot be recognized in advance; to prevent the occasional cases of fatal emetine poisoning, each patient must be considered as a possibly susceptible person. Emetine in much less than the minimal lethal dose for man is amebacidal, and emetine in very small doses, with frequent and sufficiently long rest periods, should be employed. Failure on this basis to clear up the infection indicates emetine-resisting strains of amebas, and other forms of treatment must be devised. The action of emetine on the human system is at the present time but poorly understood. Neither is its action on amebas definitely known. There is no known antidote for emetine poisoning.

Author's Summary.

Use of Dermatograms in Legal Medicine. Bettmann, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:1, 1930.

With a procedure similar to the dactylographic technic, one is able to secure exact copies of any area of the human skin during life and after death and to

study the changes of the cutaneous relief thus obtained under various circumstances. With the aid of this method, it was found that the skin in various regions of the body shows certain characteristic patterns, and that one and the same skin area examined in different persons presents definite variations. The changes in the dermatogram of the abdominal skin taken at various time intervals after death appear to be of particular interest, as they may indicate the time that has elapsed since death ensued. The different kinds of scars can be studied with accuracy, and their individual characteristics can be observed. Also, tattoo marks offer in the dermatogram certain peculiarities which can be easily analyzed and registered.

E. L. MILOSLAVICH.

VITAL REACTIONS OF WOUNDS. WALCHER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:16, 1930.

Agonal injuries, as well as those that rapidly lead to a lethal end, constantly show hemorrhages with or without fibrinous threads. Stasis and a relative dilatation of the blood vessels are occasionally observed. If life persists for fifteen minutes or more, activities of the leukocytes can be readily observed. The longer the time between injury and death, the more pronounced are the actions of the leukocytes and the changes of the nuclei of the epidermis cells (traumatic necrosis). In two hours, the inflammatory processes commence to increase gradually and become more and more pronounced with the advance of time. These reactions may be inhibited or nearly absent in instances of severe shock, in trauma of the brain and in old age. Hemosiderin appears after nine days, and hematoidin crystals are formed after eleven days. Similar reactions occur in new-born infants, with the exception that fibrin perhaps plays a smaller rôle than in adults. Postmortem and vital excoriations which do not show hemorrhagic suffusions cannot be differentiated grossly, but their character can be established microscopically. The histologic examination of the lungs in cases of drowning may disclose a more or less marked leukocytosis in the blood vessels, erythrocytes (apparently escaping from the torn septums) within the alveoli and hemolysis. Fibrinous exudation on the pleura or peritoneum following an injury, and development of pneumonic foci in instances of contusion of the lung, can be seen within several hours after the trauma.

E. L. MILOSLAVICH.

ANATOMIC CHANGES IN BRAINS OF NEW-BORN INFANTS. PH. SCHWARTZ, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:58, 1930.

More than fifty years ago, Virchow described "interstitial encephalitis" as a common cause of death in new-born and older infants. This condition is characterized by a fatty degeneration of glia cells of the white matter of the cerebral hemispheres and of the corpus callosum. These changes can be readily demonstrated in a frozen section with ordinary fat stains. One can distinguish two types of cells; namely, star-shaped cellular elements containing fat globules and round-shaped cells loaded with fat droplets. Both kinds of cells are declared to be pathologic, which is in contrast with the opinions of Merzbacher, Wohlwill, Ceelen and others. Within these areas, one may notice disintegration of the nuclei of the glia cells, degenerative changes of the axis cylinders and also disturbances of the circulation, such as stasis and minute hemorrhages surrounding the capillaries and small veins. These changes are commonly noted in stillborn infants and infants who died within the first four weeks after birth. The gross picture is characterized by punctate or linear hemorrhages in the frontoparietal portion of the white matter expanding in radial fashion (fanlike) from the wall of the lateral ventricles. Identical changes may be encountered on the cut surfaces of the occipital portion of the white matter.

E. L. MILOSLAVICH.

Technical

THE SEDIMENTATION RATE OF BLOOD IN OBSTRUCTIVE JAUNDICE. R. R. LINTON, Ann. Surg. **91**:694, 1930.

The sedimentation rate of the red blood cells is regarded as a more reliable test for the detection of a hemorrhagic tendency than any other method in cases of obstructive jaundice. Based on seventeen cases, studied before and after operation, it is concluded that an increase in the rate of sedimentation, in the absence of fever, indicates a tendency to bleed.

RICHARD A. LIFVENDAHL.

SPECIFIC GRAVITY OF URINE AS TEST OF RENAL FUNCTION. F. H. LASHMET and L. H. NEWBURGH, J. A. M. A. **94**:1883, 1930.

The determination of the specific gravity of the urine under properly standardized conditions detects a lowering of the functional power of the kidneys long before lowering is discernible by the phenolsulphonphthalein test or by the estimation of the nonprotein nitrogen of the blood.

DIFFERENTIAL BLOOD CULTURES. REUBEN OTTENBERG, J. A. M. A. **94**:1896, 1930.

Differential blood cultures are simultaneous blood cultures taken from vessels in several different parts of the body. By counting the number of colonies per cubic centimeter of blood in each vessel, it is hoped to establish from which region the bacteria are entering the blood.

That the principle is correct is shown by a study of twenty cases of sinus thrombosis or phlebitis, proved at operation or at autopsy. The principle can undoubtedly be applied to other regions of the body. In a case of suspected sinus thrombosis the finding of a much greater number of bacteria in the blood of one internal jugular vein than in the other confirms the diagnosis. But it is impossible from the count alone to tell on which side the thrombosis is located. The finding of large but equal numbers of bacteria in the two internal jugular veins with a much smaller number in an arm or leg vein also confirms the diagnosis of sinus thrombosis. Totally negative blood cultures from all three veins do not rule out sinus thrombosis. Mild cases of sinus phlebitis in which recovery can occur without tying off the jugular vein or operative opening of the lateral sinus may occasionally cause a bacteremia of the same type as that in the severe cases. Transient postoperative bacteremia is not infrequent (perhaps the result of transient phlebitis) following operations on the mastoid region in which the lateral sinus has been exposed at operation.

The finding of approximately equal numbers of bacteria in the two internal jugular veins and in the arm or leg vein indicates that the bacteria are not coming from the regions drained by any of these veins. In our limited experience (five cases) this finding occurs regularly in bacterial endocarditis, but one might expect it in many other clinical conditions, such as pneumonia or kidney suppuration. From the observations presented it is evident that the lungs and liver filter out enormous numbers of bacteria, so that relatively few of the bacteria which get into the blood stream ever reach the periphery. It would seem, therefore, that in the study of obscure infections blood cultures should be made, wherever possible, from a vein directly draining the involved region. This principle should be applicable to the study of focal infections.

The possibility exists that sudden liberation of a shower of bacteria from an infected focus can cause errors in the interpretation of differential blood cultures. It is recommended that for future investigation the multiple cultures be made as nearly as possible simultaneously. The observation that there are sometimes no bacteria detected in the blood of the arm vein, although there are bacteria in the veins directly draining the lesion, leads to the conclusion that the new type of blood cultures ought to be taken early in suspicious cases without waiting for a report of a positive result from an arm vein.

AUTHOR'S SUMMARY.

UNLAKED BLOOD AS A BASIS FOR BLOOD ANALYSIS. O. FOLIN, J. Biol. Chem. **86**:173, 179, 1930.

A revision of the Folin-Wu system of blood analysis is proposed in order to eliminate the errors, especially evident in the uric acid procedure, which arise from the presence in the final blood filtrates of products of the osmotic disintegration of erythrocytes. A new technic is described whereby protein-free blood extracts can be prepared without a preliminary laking of the blood sample. Uric acid determinations may be carried out on such extracts with a greatly improved accuracy.

ARTHUR LOCKE.

HOHN'S METHOD OF CULTURE OF TUBERCLE BACILLI. T. MATTHIES, Beitr. z. Klin. d. Tuberk. **73**:84, 1929.

The method of Hohn has been used in more than 600 experiments and has yielded excellent results.

MAX PINNER.

A NEW METHOD FOR STAINING RETICULUM. T. PAP, Centralbl. f. allg. Path. u. path. Anat. **47**:116, 1929.

Pap fixes tissues in formaldehyde and then stains frozen, paraffin or celloidin sections by a combination of the methods of Bielschowsky-Maresch, Achucarro and Foot. The various steps in the staining process are performed in the following order:

1. Aqueous, 0.25 per cent potassium permanganate; for from five to eight minutes.
2. Rinse in distilled water for from fifteen to twenty seconds.
3. Oxalic acid, 5 per cent, for from eight to ten minutes.
4. Rinse in three changes of distilled water for one minute.
5. Aqueous, 2 per cent, silver nitrate for twenty-four hours.
6. Wash in two changes of distilled water.
7. Ammoniacal silver nitrate, 1 per cent, for one-half hour. (Note.—1 grain (.065 Gm.) of silver nitrate is dissolved in 10 cc. of distilled water to which 11 drops of 40 per cent sodium hydroxide are added. The precipitate formed is then dissolved by the addition of sufficient 26 per cent ammonium hydroxide and the solution made up to 100 cc. with distilled water.)
8. Wash in two changes of distilled water.
9. Immerse in 4 per cent neutral formaldehyde for from five to fifteen seconds.
10. Wash in tap water.
11. Gold chloride solution, 0.2 per cent, five minutes.
12. Wash in tap water.
13. Sodium thiosulphate, 5 per cent, for from five to ten minutes.
14. Wash in tap water for one minute.
15. Dehydrate in series of alcohols.
16. Chloroform.
17. Mount.

This method has proved economical because four or five sets of slides may be run through the same reagents. The fibrillae are graceful because the silver apparently is reduced within them rather than on their surface.

GEORGE RUKSTINAT.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, April 24, 1930

LEILA CHARLTON KNOX, *Presiding*

ACUTE ULCERATIONS OF THE STOMACH IN CHILDREN. BENJAMIN RICE SHORE (by invitation).

An acute, fatal, perforated ulceration of the stomach wall was reported in a girl, aged 22 months. The history of ill health for only two days, the site of the ulcer on the posterior wall near the fundus of the stomach, and the lack of all signs of a chronic ulcer lead one to assume that the changes noted are of an acute and rapidly destructive nature. The markedly hemorrhagic edges of the necrotic area suggest that the primary lesion was one of hemorrhage, from either local injury, overdistention or vascular thrombosis, and that gastric digestion of this area caused the perforation. This case is of especial interest in that the perforation was found and measured at operation before postmortem digestion became manifest.

A CASE OF MULTIPLE ARTERIAL THROMBOSES. MILTON HELPERN.

Advanced arteriosclerosis occurred in a seemingly healthy white man, aged 37. Sudden death was initiated by the perforation of a duodenal ulcer which, within twenty-four hours, was complicated by acute thrombosis of the right iliac and right coronary arteries which previously had been severely damaged by the sclerotic process. The lesions in the stomach and duodenum were unusual.

The patient was admitted to the wards of the fourth medical division of Bellevue Hospital, complaining of severe pain in the upper part of the abdomen which came on suddenly several hours before. He stated that he had been troubled with "sour stomach" for two years. He said that he had not had a syphilitic infection.

Physical examination revealed a well nourished and well developed man with a normal temperature, a rapid thready pulse, poor heart sounds and tenderness and spasticity of the upper part of the abdomen. The white blood count was 8,000, with 81 per cent polymorphonuclear leukocytes. A surgical consultation was called, but the diagnosis was deferred. Several hours later, the patient complained of a numb, cold feeling in the right lower extremity. His pulse and respiration became more rapid and about two hours later he died. His illness lasted twenty-three hours from the time of its acute onset.

Necropsy revealed an acute generalized peritonitis due to a perforated duodenal ulcer. A normal-sized heart showed extensive eccentric intimal sclerosis of both coronary arteries, with a fresh thrombus occluding the right vessel about 2 cm. from its origin. The myocardium did not show evidence of recent infarction. The aorta was narrowed and exhibited a diffuse atherosclerosis with calcification. Both iliac arteries were markedly sclerosed and narrowed and the right one was occluded by a dull red thrombus, 1 cm. in length. The larger branches of the abdominal aorta exhibited a moderate intimal sclerosis. In the kidneys microscopic examination revealed a mild degree of arteriolosclerosis with an occasional hyalinized glomerulus, but the parenchyma, on the whole, was well preserved. Histologic examination of numerous sections through the coronaries, the aorta and the iliac arteries confirmed the gross observations.

The stomach was interesting both grossly and microscopically. It was greatly enlarged, although contracted. The entire mucosa was markedly hypertrophied and the rugae were extremely prominent. In the anterior wall of the duodenum,

near the poorly defined pyloric duodenal junction, there was a perforated, punched-out, triangular, funnel-shaped ulcer with reddened and elevated mucosal edges measuring 1 cm. on each side. On the serosal aspect, a mound of granulation tissue surrounded the slitlike perforation of the thin fibrous base. To the right of the perforated ulcer there was a smaller deep ulcer; distally there were several pitted erosions in the mucosa, which were seen on microscopic examination to extend down to the subserosa. The blood vessels along both curvatures did not appear grossly abnormal, except for an intense congestion of all the vessels incident to the acute peritonitis.

Numerous sections of the stomach were taken through the ulcers and also at intervals along the lesser and greater curvatures from the cardia to the pylorus. The mucosa was markedly hypertrophied, and most of the serosal arteries showed a mild degree of eccentric intimal thickening. An artery in the base of the perforated ulcer was occluded in some sections by an adherent thrombus, and in other sections by a proliferation of endothelium into the lumen. Seven millimeters from the edge of the nonperforated ulcer, in the thickened submucosa, there was a thickened vessel showing a marked obliterating endarteritis.

The most striking vascular lesion was found in a section through the lesser curvature of the stomach, 6 cm. proximal to the perforated ulcer. In the serosa there was an artery with a media of normal thickness and with a lumen completely occluded by the organization and canalization of an old thrombus. This vessel presented a solid appearance much resembling a nerve, but the presence of a well preserved internal elastic lamina, several canalizing vessels with their elastic laminae and a few scattered particles of blood pigment indicated that the structure was an organized and canalized thrombosed artery. In one section taken 14 cm. proximal to the ulcer, a very small serosal artery showed a marked concentric intimal thickening with the formation of a new internal elastic lamina. In all the sections studied, the submucosal vessels were well preserved. Bacterial and spirochetal staining of the various tissues gave negative results except for a few scattered cocci on the acutely inflamed peritoneum.

It is not altogether unlikely that the ulcers in this case may have followed nutritional disturbances due to the distant thrombosed vessel. In infarct formation elsewhere, the process commonly occurs in tissues removed from the immediate point of vessel occlusion depending on the distribution of the end arteries.

DISCUSSION

PAUL KLEMPERER: Were these thrombosed vessels found in all the sections of the stomach? Were they found in the serosa?

MILTON HELPERN: The organized thrombosed vessel was seen in the serosa in one section, about 6 cm. proximal to the ulcer. The other serosal vessels showed moderate intimal thickening, but were not thrombosed. There was considerable intimal thickening in the section taken about 14 cm. proximal to the ulcer near the esophageal junction. Sections from the greater curvature also showed moderate thickening of the intimal layer. All these vessels were found in the serosa.

PAUL KLEMPERER: These changes are unusual, and I am not inclined to consider them as multiple atherosclerotic thromboses. The intima was thickened, and in only one of the sections did I see what I thought was interference with the elastica. Are not the lesions in the stomach unusual for atherosclerosis?

MILTON HELPERN: The designation of multiple arterial thromboses in the title referred more to the thrombi in the iliac and coronary arteries. There was a moderate degree of ordinary arteriosclerosis in the vessels of the stomach, but as Dr. Klemperer pointed out, the other vascular lesions were unusual for arteriosclerosis. In all the sections through the arteries it was possible to trace the elastic lamina, although it was interrupted in places. Just what the etiology of the organized thrombosis in the artery on the lesser curvature was, we do not know, but the lesion was evidently not a recent one. Of course, the other partially thrombosed vessel in the base of the perforated ulcer which was occluded by an endothelial proliferation might be considered a reaction to the ulcer.

CLARENCE DE LA CHAPELLE: As Dr. Klemperer pointed out, the picture of the vessels in the stomach does not look like ordinary arteriosclerosis. It brings up the point as to the frequency of ordinary arteriosclerosis in the gastric vessels. In young persons, according to Ophüls, arteriosclerosis in the gastric vessels alone is a common observation; however, in this patient there was a generalized arteriosclerosis. It is unfortunate that he did not live a week or so longer so that one could have seen what developed in the clinical picture with regard to the thrombi. It would have been of great interest to see what the outstanding clinical signs were.

PAUL KLEMPERER: Of course, severe atherosclerosis in the stomach is unusual. We have examined a considerable number of stomachs in cases of nephrosclerosis, because we were interested in the condition of the vessels throughout the body. I do not remember the actual figures, but a very small number of these cases showed lesions in the stomach similar to those in the kidneys and pancreas. In routine material, even in cases of severe atherosclerosis, one finds that the stomach is frequently spared. There is no question but that the lesions in the coronary artery and iliac vessels are atherosclerotic. The question still remains in my mind whether the lesion in the stomach is atherosclerotic or not. Of course, the absence of a similar lesion in the submucosa speaks against the possibility that there is a previous inflammation of the stomach responsible for the arterial damage. In healed phlegmonous gastritis, I should imagine, similar lesions could be produced, but one would expect them in the submucosa. It still remains a question whether the lesion in the stomach vessels is of the same nature as the atherosclerosis in the iliac vessels.

One point deserves some discussion. It was interesting to hear that Dr. Helpern believes that the thrombosis in the vessels was due to the peritonitis. One can imagine that the toxemia brought about the thromboses. The question might be asked, why is it that in severe atherosclerosis one sometimes finds thromboses but that more frequently one does not find them? There must be an additional factor present to cause the thrombosis. One can realize that the toxemia in peritonitis causes some immediate acute endothelial damage, and that this leads to thrombosis. One can think of the explanation suggested by Dr. Libman, that some of the cases of coronary thrombosis in subjects with severe atherosclerosis may be due to a sudden rise in the blood platelets. Such attacks of thrombocytemia seem to occur. I do not think that this has even been actually followed up clinically. I remember one case that suggested this possibility, in which the patient had a platelet count of over 400,000. I observed other cases in which there was no question but that venous thrombosis was caused by thrombocytemia. In a few cases in which the thrombotic tendency was evident I have examined the bone-marrow to find whether there was an increase in the megakaryocytes present. I do not think that I have any definite evidence, but it might be worth while to examine the bone-marrow in cases in which a thrombotic tendency exists.

MILTON HELPERN: The organized thrombosed vessel in the stomach certainly does not seem to be the same type of lesion as that found in the sclerosed vessels elsewhere. Apparently it appeared some time before, judging by the canalization that took place in the obliterated lumen. This lesion would therefore not have any relation to the sudden pain that ushered in the patient's last illness.

Regarding a hypertrophic gastritis following a phlegmonous gastritis, that does not seem likely from the sections. There was no scarring. The mucous membrane was hypertrophic, but otherwise in excellent condition. The submucosa appeared intact and the submucosal vessels normal. In this case the kidney, surprisingly enough, was well preserved. There were only one or two small arterioles that showed any thickening at all, and the parenchyma was in a good state of preservation, whereas the lesions in the stomach seemed to be extensive. The etiology of the old thrombotic lesion in the artery on the lesser curvature is not clear. The more recent thrombotic lesion in the vessel in the base of the perforated ulcer might be considered as secondary to the ulcerative process. Thickened and sometimes thrombosed vessels are not infrequently found in the base of ulcers.

A Case of So-Called Acute Isolated Myocarditis (Subacute Productive Myocarditis). Clarence de La Chapelle and Irving Graef.

Recently, Scott and Saphir reported the first two cases of acute isolated myocarditis to be recorded in the English language. In their paper they mentioned reports of thirty-six other cases recorded in the Continental literature since 1888, when Steffen described two cases of acute myocarditis which probably belonged in this group.

It has been noted by practically all authors that the outstanding clinical feature is progressive myocardial insufficiency. In none of the cases has the etiology been demonstrated, nor have any cases been diagnosed correctly during life.

The following case is reported in order to add another example of what appears to be Fiedler's myocarditis to the small group already recorded.

A. M., a white laborer, aged 21, born in Argentina, was admitted to Bellevue Hospital, third (New York University) medical division, on Jan. 25, 1930, complaining of pain in the chest and dyspnea. His family history was irrelevant. He gave a history of occasional colds, but no history of polyarthritis or venereal disease.

The patient appeared chronically ill, but well nourished. He had slight dyspnea, orthopnea, and a café-au-lait color. The sclerae were icteric. There were pulsating veins in the neck and one of the superficial veins of the left arm could be seen pulsating. The apical beat of the heart was visible and palpable in the sixth space, 14 cm. from the median line, at a point in the anterior axillary line. A 2 meter roentgenogram of the heart, taken five days after admission, showed marked enlargement in the transverse and long diameters. The first sound at the apex was of poor muscular quality. The sounds at the base were faintly audible. The rhythm was regular. The heart rate was 92 per minute. The radial pulse was small; it could not be palpated on the left side, owing to edema of the arm. The blood pressure was 105 systolic and 82 diastolic. There were signs of fluid over the area of the right lower lobe, with crepitant and subcrepitant râles and dulness above the eighth rib posteriorly. The edge of the liver was palpable 8 cm. below the costal margin; it was tender but did not pulsate. The spleen was not palpable. There was no evidence of ascites. Both lower extremities presented slight edema.

On admission, examination of the blood showed 10,400 leukocytes, with 79 per cent polymorphonuclears, 20 per cent lymphocytes and 1 per cent transitionals. The red blood cells numbered 3,700,000 with 70 per cent hemoglobin. The Wassermann reaction of the blood was negative. Blood cultures taken on two different occasions yielded no growth. The systolic blood pressure never exceeded 112; the diastolic ranged between 82 and 92. Electrocardiograms revealed prolongation of the P-R interval (from 0.2 to 0.24); there was complete intraventricular block of the right bundle branch; there was low voltage in all three leads; normal sinus rhythm was present. Examination of the sputum revealed an unclassified pneumococcus. On the patient's admission to the hospital the urine was normal; subsequent examinations revealed a slight albuminuria and the appearance of numerous hyaline and finely granular casts; an occasional red blood cell was found on one occasion, the day before death. Blood chemistry tests performed two days after admission showed 64 mg. of nonprotein nitrogen and 119 mg. of sugar per hundred cubic centimeters. Three days before death the nonprotein nitrogen was 100 mg. and the creatinine 4.7 mg. per hundred cubic centimeters.

The temperature ranged between 98 and 100 F., and the pulse rate between 68 and 100 per minute. Thoracentesis was performed two days after admission, yielding 80 cc. of clear straw-colored fluid with a specific gravity of 1.008. The cell count was 1,940, the differential count including chiefly lymphocytes and endothelial cells. The patient progressively gained weight, with increasing edema of the lower extremities and of the left arm and hand. Facial edema became marked about four days before death. There was no change in the cardiac observations. Cyanosis, which was of a fairly marked degree, was intermittent. During the last few days, as the congestive heart failure became more marked, slight icterus,

oliguria, Cheyne-Stokes' respiration and stupor supervened. The patient died twelve days after admission to the hospital, presenting a picture of heart failure and uremia.

Necropsy showed a well nourished and well developed white man, aged 21. Except for moderate pitting edema of the legs, trunk and left arm and slight icterus of the skin and sclerae, external examination gave negative results. The peritoneal cavity contained about 500 cc. of clear straw-colored fluid. Each pleural cavity contained about 300 cc. of clear fluid. The pericardial sac contained about 75 cc. of clear fluid. Otherwise the serous sacs were intact.

The heart was large, weighing 600 Gm. Its external measurements were 16 by 13 by 9 cm. It was so soft and flabby as to spread like a mushroom over the supporting hand. All the chambers were markedly dilated. The papillary muscles of both ventricles were flattened. The mitral valve and its chordae tendineae were normal. The valve orifice measured 10 cm. in circumference. The aortic orifice measured 6 cm. in circumference; the cusps were normal. The tricuspid orifice measured 11.5 cm. in circumference; the valve and its chorae tendineae were normal. The myocardium of the left ventricle measured 18 mm. in thickness at the base of the ventricle, 10 mm. near the apex and from 2 to 3 mm. at the apex. The right ventricle measured 6 mm. in thickness at the base and 3 mm. at the apex. The epicardium was normal, except for a few smooth, glistening points of thickening, the size of a pinhead, over the right auricular appendage. The endocardium was intact throughout except at the apex of the left ventricle, where a firm, grayish-red thrombus was found attached to the endocardium. The right auricular appendage was filled by a firm, attached, grayish-red thrombus.

On section, the myocardium, particularly that of the left ventricle, appeared remarkably altered, brownish and brownish-yellow streaks being scattered throughout; nearby were seen irregular bands of gray and grayish-yellow firmer tissue. The linear markings of the muscle bundles, on section, were barely visible. The coronary orifices and arteries were normal.

Both lungs were heavier than normal; the pleural surfaces were smooth. The cut surface was reddish blue and oozed frothy serosanguineous fluid; they were otherwise normal. The liver weighed 1,300 Gm. The capsule was smooth. The cut surface was firm, showing the markings of chronic passive congestion, which gave the organ a nutmeg appearance. The spleen was normal in size and shape, weighing 220 Gm. On section, the pulp appeared firm and red, and the follicles fairly prominent. The kidneys were somewhat enlarged, weighing 420 Gm. together. The capsules stripped easily, leaving a smooth surface. On section and inspection they were normal except for slight hyperemia and one small grayish, apparently healed infarct in the right kidney. The pancreas, suprarenal glands, bladder, prostate and testes appeared normal.

Sections were taken from both ventricles, both auricles, the auricular appendages, valves, papillary muscles, aorta and pulmonary artery. The stains used were hematoxylin-eosin, van Gieson's, Mallory's connective tissue, Weigert's elastic tissue, sudan III, Nile blue, Gram-Weigert's methyl-violet, Unna-Pappenheim's, Levaditi's and Warthin-Starry's stains.

Sections from various portions of both ventricles revealed marked hypertrophy of the muscle nuclei and fibers, both of which were many times larger than in normal circumstances. The interstitial connective tissue was increased in amount. Newly formed blood vessels were abundant and were injected. They were seen growing into and between muscle bundles and fibers.

The lesion noted was widely distributed and more marked in the myocardium of the left ventricle. Areas of considerable dimension were found consisting of degenerated, edematous muscle fibers and nuclei, infiltrated by large numbers of lymphocytes, endothelial cells, fibroblasts and newly formed blood vessels. These areas were irregular in outline and poorly demarcated; they did not present a constant picture, as the several elements varied in number and location. In some places there was an abundance of young connective tissue cells with a few lymphocytes and an occasional plasma cell; in other places focal collections of

lymphocytes, a few plasma cells and large endothelial cells were found in and around edematous muscle fibers. Some of the endothelial cells presented sharply outlined nuclei, and in their cytoplasm a fine granular pigment was occasionally seen. No giant cells or Aschoff bodies were found in any of the sections. One coronary arteriole was found to contain a partial parietal thrombus composed of fibrin, in the meshes of which a few leukocytes could be seen. Near the well marked areas of inflammatory reaction, small focal areas of muscle necrosis were encountered, with no surrounding inflammatory reaction. The cross-striations of the muscle fibers were normal, except in the areas of degeneration. Fat was not markedly increased in amount; with the sudan III stain it could be seen in fine droplets in most of the myocardial fibers. Sections stained by the van Gieson and Mallory connective tissue methods showed scattered foci of fibrous connective tissue. These were chiefly interstitial. With these stains the interstitial elements in the areas of muscle degeneration were seen as fine fibrillar bands with no intervening stained sarcoplasm. Polymorphonuclear leukocytes and eosinophils were scarce. No areas of hemorrhage were seen. At the apex of the left ventricle, section revealed a fairly advanced organizing process involving the endocardial thrombus and the adjacent muscle. Sections of the valves and endocardium, except at the apex, as noted, revealed a normal structure. Sections of the aorta and pulmonary artery showed no changes. The stains for amyloid, bacteria and spirochetes yielded negative results. Sections from the other organs confirmed the anatomic diagnosis.

Progressive heart failure was the outstanding clinical feature in this case. This is in accord with the observations of previous authors. Of great clinical interest is the data obtained by electrocardiograph, which gave further evidence of the extensive distribution of the lesion, i. e., first-stage auriculoventricular block and complete intraventricular block of the right bundle branch variety. Careful search for an etiologic factor revealed nothing. There was no history of any of the well known infectious diseases, including rheumatic fever, diphtheria, scarlet fever, syphilis or tuberculosis, nor were we able by any means available to demonstrate an etiologic agent post mortem. The exact onset of the lesion in this case is doubtful. The embolic phenomena noted during life and their evidence at necropsy are particularly noteworthy and possibly give a clue as to the onset and duration. Thus, the cerebral accident about eight and one-half months before death, the healed infarct in the kidney and the probable pulmonary infarct about six weeks before death suggest that the intracardiac thrombi were present for some time.

A detailed report of this case will be published.

DISCUSSION

CLARENCE DE LA CHAPELLE: From a clinical point of view this case was interesting and most unusual; as is noted, no diagnosis was made. We knew that we were dealing with congestive heart failure, but in the absence of a history of any of the usual causes of heart disease, we had no etiologic factor. We were unable to correlate our observations on progressive marked heart failure in a subject aged 21 with those in any of the ordinary types of acute heart failure. I refer to those associated with rheumatism, subacute bacterial endocarditis and diphtheria. We could see from the electrocardiographic observations that there were extensive changes in the muscle. We therefore inferred that we were dealing with an unknown form of heart disease showing marked enlargement and no signs of pericardial or valvular disease. The first physician to see the case thought of lobar pneumonia, as the patient gave a history of cough and spitting of blood. Another diagnosis was acute pleuritis. The possibility of subacute bacterial endocarditis was thought of, because the patient had a distinct café-au-lait color, but he had no clubbing of the fingers, splenic enlargement or petechiae. As to the possibility of rheumatism, there was no history and no clinico-anatomic evidence of rheumatic fever. The outstanding feature was the confusion in diag-

nosis owing to the absence of an etiologic factor and the rapid downhill course despite treatment.

From the pathologic point of view, we report the case because it is unusual, only two other cases having been reported in the English language. A total of thirty-eight cases has been recorded in forty-two years. Possibly other cases have been observed but not reported. This disease may be more common than we think it is. It makes one wonder, after seeing the changes microscopically, and particularly the last two slides in which there were practically no cellular elements — merely fibrous replacement — what the end-result of this disease might have been if the patient had lived a little longer. I think that we have a partial answer to this. About three months before the present meeting an autopsy was performed by the medical examiner on a boy of the same age as the one in our case. He was a messenger who dropped dead while delivering a package. At autopsy everything appeared normal except the heart, which showed only a diffuse replacement fibrosis. The coronary arteries were normal. There was no inflammatory lesion on the valves, myocardium or pericardium. There was a healed osteomyelitis of the right radius, which was definitely an old lesion. The disease may have been similar to that in the present case, possibly the end-result of the same process.

M. A. KUGEL: Were any lesions noted in the neuromuscular bundle?

IRVING GRAEF: One section through the bundle showed no change located directly in it. There were changes near it.

PAUL KLEMPERER: This case reminds me of two cases, one of which apparently conforms fully to the description of Dr. de La Chapelle's second case. In this case, which I observed many years ago, a young boy died suddenly; at autopsy we found the same picture: a diffuse fibrosis without any etiologic clue. The Wassermann test performed on the blood of the cadaver gave negative results. The other case, in which I performed autopsy only six months before the present meeting, may have possibly shown a more acute stage of the same disease. I say "possibly" because we have no other explanation for it. In this case a woman, aged 32, underwent splenectomy for thrombocytopenic purpura two years before her death. Two months before death hemorrhagic diathesis again developed, for which ergot was given. She was then admitted to the hospital with profound anemia; a transfusion of blood was given, and she died rather suddenly. It was thought that death was due to anemia; however, the heart presented distinct gross lesions and smaller and larger areas of grayish color; contrary to the present case, histologic examination revealed chiefly polymorphonuclear leukocytes. Bacterial stains, including Gram's stain, gave negative results. We found no other evidence of inflammatory lesions throughout the body. The spleen had been removed, but, from the anatomic standpoint, there was no evidence of a septic condition. Examination of the heart blood was omitted because of our experience with postmortem bacteriology. This case may have represented an early stage of the condition under discussion. It is possible that if the patient had lived longer, the acute inflammation would have changed into the picture of a granulation tissue as in the case reported. The patient died of anemia. There had been no outstanding cardiac symptoms during her life.

CLARENCE DE LA CHAPELLE: In reference to the cellular reaction in Dr. Klemperer's case, it is interesting to note in the other cases reported that there does not seem to be any characteristic histologic picture. A few describe polymorphonuclear leukocytes and a few mention giant cells, but there does not seem to be any uniform picture.

PAUL KLEMPERER: Of course, one has to be careful in searching through the other organs. I had a third case which was just as puzzling as those mentioned. The heart presented a picture that reminded one of Fiedler's myocarditis because of the localization of severe inflammatory lesions in the myocardium without endocardial or pericardial involvement. There were some giant cells, but the same changes were found in the spleen and liver.

ANOMALOUS ORIGIN OF THE RIGHT SUBCLAVIAN ARTERY. VERA B. DOLGOPOL.

In a woman, aged 36, the branches of the aortic arch were: (1) the right common carotid, (2) the left common carotid, (3) the left subclavian and (4) the right subclavian. The innominate artery was missing. The origins of the first three branches were situated on the anterior aspect of the aortic arch; the right subclavian artery arose on the posterior aspect of the aortic isthmus. The course of the right subclavian artery was behind the trachea and the esophagus, on the vertebral column in the region of the third and second dorsal vertebrae and then over the dome of the right pleura. It passed in front of the scalenus anterior, and from then on the course and the branches of the artery were normal.

The portion of the right subclavian artery between its aortic origin and the scalenus anterior is a remnant of the right dorsal aortic root.

The anomaly did not give any symptoms during the patient's life.

Stated Meeting, May 22, 1930

LEILA CHARLTON KNOX, *Presiding*

PLACENTA INCRETA. BORIS KWARTIN and NATHAN H. ADLER.

Placenta accreta and increta are among the most serious complications of the after-birth period. The authors were able to collect only seventy-four cases in the literature. One case came under their direct observation which was of great interest because of the clinical history and pathologic anatomy, which resembled those of tubal pregnancy.

A secundigravida, unipara, 28 years old, was admitted for cesarean section two weeks before term with symptoms of threatening rupture and complaining of severe abdominal cramps and a dark brown, bloody discharge. She had had a cesarean section two years before with postpartum endometritis and pneumonia. At operation the placenta was found to be adherent, for the greater part at the site of the old scar, and a hysterectomy was performed. The patient made an uneventful recovery. On pathologic examination, grossly, the chorionic villi were seen to extend deep into the muscularis, and in the region of the previous scar, with no muscle fibers, the chorionic villi penetrated to the serosa. Microscopically, the decidua was completely absent in the region of the placental inflammation. The chorionic villi broke through the hyaline layer of Nitabuch. In places the cells of the upper layers of the muscularis showed a decidua-like transformation. Elsewhere the decidua vera was almost completely absent.

The etiology of placenta accreta is still debated on the following points:

1. The most important factor is the condition of the uterine mucosa at the time of nidation of the ovum. Maldevelopment of the uterus, an infantile uterus with hypoplasia of the endometrium, repeated curettages, septic endometritis, diverticular pregnancies, atrophic endometrium above the uterine myomas, and the persistence of operative scars from previous cesarean sections are etiologic factors of great importance.

2. A primary tendency toward excessive growth on the part of the chorionic villi is another etiologic factor.

3. Insufficient production of antiferment against the arrosive power of the trophoblasts, possibly owing to the deficiency in the hormonic cycle of the maternal organism, is a third factor in the etiology of placenta accreta.

DISCUSSION

ALFRED PLAUT: This is a clearcut case of placenta increta. In years of experience in gynecologic pathology I have more frequently seen placenta increta diagnosed and not found than not diagnosed. Often the clinician says that the

removal of the placenta has been difficult, or that some hard things have been felt while the placenta was being removed, but the diagnosis should not be made unless the chorionic villi are seen directly on the myometrium or growing into it without any spongy layer between. The demonstration by Dr. Kwartin showed a typical case of true placenta increta.

ARTERIOLAR NECROSIS OF THE KIDNEY. PAUL KLEMPERER and SADAO OTANI (by invitation).

Essential hypertension with renal insufficiency is associated with atherosclerosis of slow progress, with gradual constriction of the vascular bed and subsequent advanced destruction of the functioning parenchyma or with a more rapidly developing vascular alteration without severe renal atrophy. The latter form, the malignant phase of hypertension, must be divided pathologically, according to the nature of the vascular lesions, into an accelerated atherosclerotic and an arteritic form.

The rapidly developing constriction of the vascular bed, which cannot be overcome by the maximal elevation of the blood pressure, is responsible for the sudden onset of the fatal renal insufficiency.

The etiology of the vascular condition has not been determined. The pathologic picture and clinical analysis suggest that the accelerated atherosclerotic form may be caused by a constitutional or acquired angiospastic factor. The arteritic form is most probably caused by the influence of various toxins on the vessels already affected by a degenerative simple atherosclerotic process.

This paper will appear in full in a future issue of the ARCHIVES.

DISCUSSION

ALFRED PLAUT: How far were the corresponding arteries in other organs, notably in the pancreas, the spleen and the suprarenal glands, observed?

PAUL KLEMPERER: In all of our cases we found arteriolosclerosis in one or the other organs, mainly in the pancreas, the liver and the suprarenals, in about the same percentage as one used to find it in simple hypertension. The spleen cannot be taken into consideration because of the extreme frequency of arteriolar hyalinization found in this organ during routine examination. We examined the abdominal muscle and the diaphragm in the last six cases only, and we did not find any arterial lesion, either in the intima or in the media, as claimed by Keith and Kernohan.

Regarding the type of vascular alteration, we seldom found cellular intimal thickening in other organs than in the kidneys, except in the choroid where we found it in every case in which the eye had been examined.

BENJAMIN SACKS: Some years ago Dr. Baehr and I reported before this society several cases of endocarditis of a peculiar type in which there was a necrotizing arteriolitis of the kidneys similar to that in one of the cases that Dr. Klemperer illustrated on the screen. In this particular case we searched in vain for Aschoff bodies in the heart. We finally were forced to come to the conclusion that this type of verrucous endocarditis was similar in many respects to that which is seen in rheumatic cases, though such an etiology could not be established, and we had to put the case in the atypical group. All of the patients in our three cases died of uremia.

ARTHUR M. FISHBERG (by invitation): Dr. Klemperer brought up the point that there is a difference of opinion as to whether so-called malignant hypertension is always preceded by "benign" hypertension. He is not convinced that there is such a preceding stage, and I gather that he believes that there usually is not. I personally am of the contrary opinion, and I think that the so-called malignant hypertension is merely one of the phases of essential hypertension, which invariably follows a period of hypertension clinically and anatomically characterized by the features we are accustomed to associate with "benign" hypertension. The following evidence favors this view: First, the clinical histories of many of these

patients show that asymptomatic hypertension had been present for some years—for two or three years or even considerably longer. Furthermore, on the first examination of these patients, albuminuria is often absent and may be missing for years. I am referring to the patients who when seen years later at necropsy exhibit the typical necrotizing arteriolar lesions in the kidney that Dr. Klemperer has so well demonstrated. Despite the fact that some of these patients, when first examined, have no albuminuria, we often know that some day they will come to necropsy with necrosis of the renal arterioles because of the presence of characteristic changes of the eyeground with papilledema. Whenever you see these ophthalmoscopic changes with papilledema in a patient with essential hypertension, you can predict, with a high degree of confidence, that at necropsy you will find necrosis of the renal arterioles. The fact that at this stage these patients have no albuminuria seems to me good evidence that there is no necrosis of the renal arterioles with its inevitable consequences to the glomeruli. At this period, the renal changes can be at most those of arteriolosclerosis, else the patients would have albuminuria. As Dr. Klemperer has brought out very clearly, in kidneys with arteriolar necrosis, one usually does not find a great number of hyalinized glomeruli, and the hyaline changes in the arterioles of the kidney are generally not excessive. However, these changes are always present to some extent and are sometimes marked. Moreover, one finds arteriolosclerosis in the pancreas, the liver, the spleen and other organs. One does not find necrosis, but only arteriolar sclerosis in these organs. The mere fact of the presence of this arteriolosclerosis with its characteristic distribution points to a long-standing hypertension. For these reasons, I regard malignant hypertension as a phase of essential hypertension. I cannot explain why only a small proportion of patients with essential hypertension advance into the malignant phase. However, one can see that youth is a strong predisposing factor; the average age of death of patients with necrosis of the renal arterioles is much younger than that of other sufferers from essential hypertension. The situation is analogous to that in diabetes mellitus, in which the younger the patient, the more severe the disease is apt to be. But quoting an analogy does not explain the phenomenon.

PAUL KLEMPERER: The question of Dr. Fishberg's discussion is, of course, the one that puzzled us most. There is no doubt, and I hope that every one understood me, that all of our patients had a preceding stage of hypertension. On an average this lasted, as far as we know, for about two and a half years. We had one patient who was refused life insurance, three years before his death, because of elevated blood pressure. He was examined at that time at the Cornell Clinic, and his urine was found to be free from albumin. After an interval of nearly three years the clinical picture became serious, and he died of uremia. It is possible that this is the longest duration of the malignant form of nephrosclerosis, but it is also possible that this patient had had hypertension a long time before it was actually detected. We do not know, either, how long the lenta form of nephrosclerosis lasts. It is evident, however, that it lasts much longer than three and a half years.

The question is whether or not in the malignant form, the atherosclerotic process advances from the very first at a more rapid tempo than in simple hypertension. It is, of course, evident that even with a rapid development of the atherosclerosis there is not immediately a complete constriction of the blood vessels leading to renal insufficiency and necrosis of the arterioles, and it is conceivable, therefore, that in the first years of such a development the clinical picture will in no way be different from cases in which the atherosclerosis develops slowly. The main fact on which one must base one's opinion that atherosclerosis in the malignant form starts from the first at a more rapid tempo and need not go through a period of slow progress is the more extensive atrophy of the parenchyma which one finds in such cases, in contrast to that found in the early forms of simple arteriolosclerosis. In this instance the tubular atrophy is dependent on glomerular fibrosis. In our observations there is an incongruity between glomerular lesions and parenchymal atrophy.

Book Reviews

HYPERTENSION. By LESLIE T. GAGER, M.D. Price, $3. Pp. 158. Baltimore: Williams & Wilkins Company, 1930.

In this book Gager reviews the important work on hypertension in the past few years. He believes that hypertension is a "primary disorder of vasomotor function," and traces briefly the development of knowledge of hypertension from Traube's first description of increased arterial tension in 1856 to the present time. Adequate consideration is given to the various etiologic factors that other workers have championed. A chapter is devoted to the relation of hypertension to renal disease and another to various chemical factors that have been considered by some to bear on the etiology. Gager does not, however, express his opinion as to either and leaves an impression with the reader that he does not consider them important as causative factors. In the chapter on the functional basis of hypertension he gives his own ideas clearly. He holds that the so-called "stress and strain" of modern civilization play an important part in the development of hypertension. Statistics are cited revealing that hypertension among certain tribes of African natives is extremely rare, although their diet consists mainly of meat, and chronic infections are frequent. The symptomatology and the incidence of hypertension are considered fully. In clinical work Gager stresses the importance of studying the retinal vessels to determine the stage and to follow the progress of the disease. Because only a small percentage of patients with hypertension die of renal insufficiency, Gager emphasizes the importance of signs pointing to the more frequent occurrence of death from cardiac or cerebral conditions as well as the more easily obtained tests of renal function. Prognosis is dealt with mainly from a statistical standpoint. The author believes that much can be done for patients in the early stages of elevated systolic pressure. Knowledge of the patient's personality, environment, heredity and adjustment in the mode of living is especially helpful. Moderate exercise in some cases, a simple diet and the reduction of weight in the obese are also recommended in this group. Gager has used the sulphocyanates with better results than obtained with other drugs, and potassium iodide and bromide in combination are the next most effective. The book gives a concise yet comprehensive presentation of the recent investigations in this field.

TEXTBOOK OF PATHOLOGY. By DHIRENDRA NATH BANERJEE, M.D., Demonstrator of Pathology, Carmichael Medical College; Radiologist, Chittaranjan Hospital; Radiologist, Calcutta Polyclinic, Ltd. Second edition. Pp. 636, with 305 illustrations and 9 colored plates. Calcutta: The Medical Bureau, 1929.

As an outline of pathology and allied subjects, to be properly supplemented by comprehensive lectures, this text should be very useful to students, not only in the Orient, but elsewhere. The author has attempted to cover morphologic pathology, bacteriology, animal parasitology, laboratory methods in general and epidemiology — all in one volume. In addition, he correlates the morphologic observations in each disease condition with the pathologic physiology and the clinical picture. Therefore, the presentation of the various topics is of necessity rather sketchy, and of doubtful value to those approaching the subject for the first time. A few diseases are treated in more detail, especially those that are prevalent in the East, such as malaria, kala azar and the dysenteries. For the most part the author's point of view on disputed subjects is orthodox, although he has accepted the newer use of the term nephrosis to include all types of renal degeneration not accompanied by inflammatory changes. His discussion of the etiology of atherosclerosis reveals familiarity with the results of recent experimentation; in fact, most of the subjects are brought well up to date.

Probably the least convincing parts of the book are the lists of definitions, many of which are not entirely accurate in detail. For example, congenital and hereditary diseases are not clearly differentiated, and the only hereditary disease mentioned, namely, hemophilia, is classed as pseudohereditary. However, in spite of a few such defects, the book may well be a valuable addition to the medical student's library.

THE CREED OF A BIOLOGIST. A BIOLOGIC PHILOSOPHY OF LIFE. By ALDRED SCOTT WARTHIN, PH.D., M.D., LL.D., Professor of Pathology, University of Michigan. Cloth. Price, $1.50. Pp. 60. New York: Paul B. Hoeber, Inc., 1930.

This is a frank and dignified statement of a philosophy of life which has brought deep inward satisfaction to the author. The good of the race, the progress of the race and the future welfare of the race loom large in his mind and credo. The transmission of acquired characters is a leading article of faith, and the author stands firm in his conviction that the course of evolution can be determined by man's will. It may occur to some readers that if the inheritance of acquired characters were as well established by scientific evidence as, say, the mendelian law, no one would feel called on to express a "belief" in it.

The purpose and spirit of the book as a whole are admirable and will unquestionably touch sympathetic strings in many persons. Not all men are born believers, and there should be a place somewhere for those who feel the impulse of the ironic smile, but do not want to "commit suicide." And is it so certain that all the evils in the world are man's and none nature's?

Books Received

A System of Bacteriology in Relation to Medicine. Medical Research Council. Volumes 1 to 5. Cloth. Price, per volume, 1 pound, 1 shilling, net. London: His Majesty's Stationery Office, 1930. (May be obtained from the British Library of Information, 551-5th Avenue, New York.)

Hypertension. By Leslie T. Gager. Cloth. Pp. 160, with illustrations. Price, $3. Baltimore: The Williams & Wilkins Company.

A Compilation of Culture Media for the Cultivation of Micro-Organisms. By Max Levine and H. W. Schoenlein. Cloth. Price, $15. Pp. 969, with 7,000 formulas and four indexes. Baltimore: The Williams & Wilkins Company, 1930.

Naissance, vie et mort des maladies infectieuses. By Charles Nicolle, Directeur de l'Institut Pasteur de Tunis. Prix Nobel de Médécine 1928. Paper. Price, 15 francs. Pp. 219. Paris: Librairie Félix Alcan, 1930.

Die Wechselbeziehungen zwischen der Tuberkuloseerkrankung und den Generationsvorgängen im weiblichen Organismus. Von Privatdozent Dr. Joachim Granzow, Oberarzt der Staatlichen Frauenklinik Danzig-Langfuhr. Paper. Price, 10.80 marks. Pp. 196, with 28 illustrations. Berlin: S. Karger, 1930.

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ARCHIVES OF OPHTHALMOLOGY—Monthly. Includes original articles on diseases of the eye, abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 85 cents.

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